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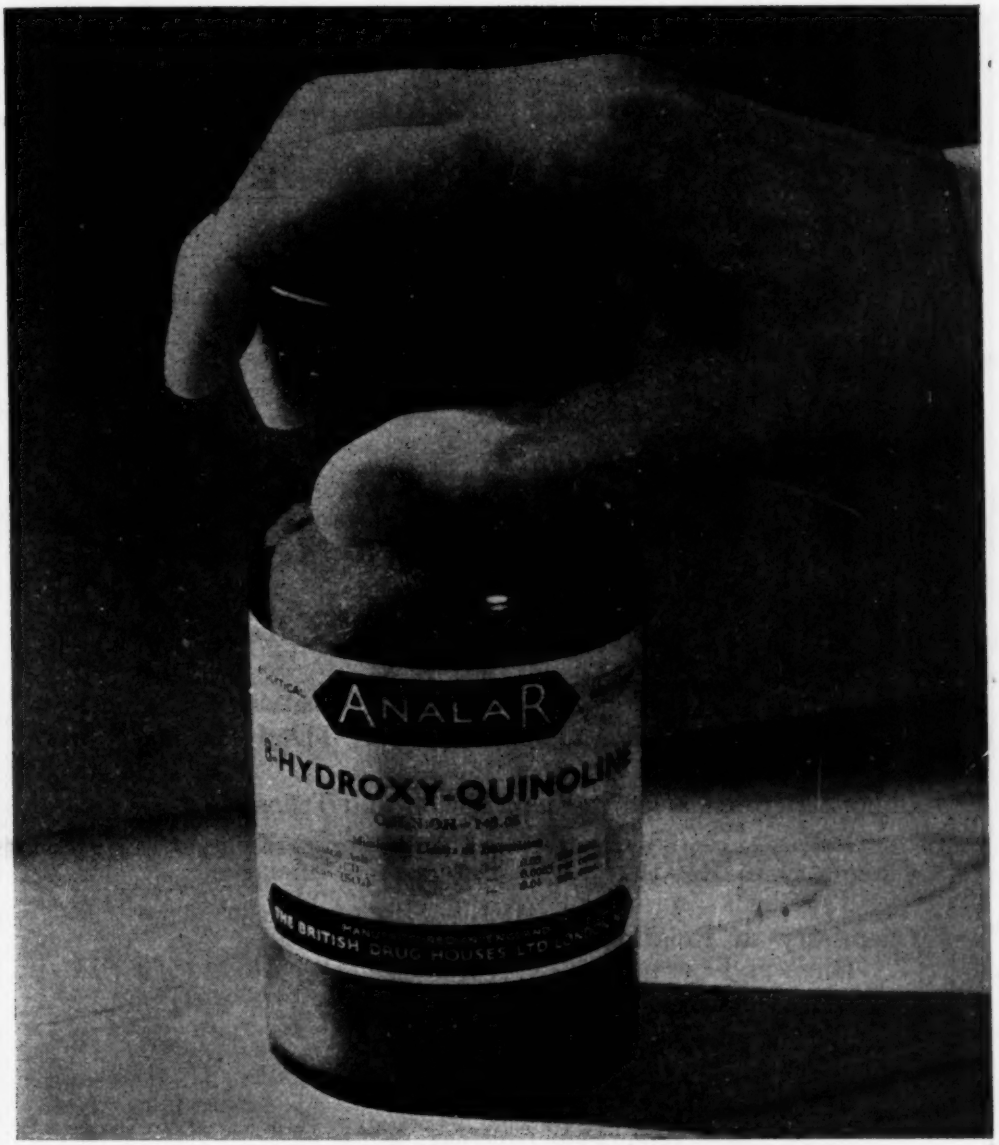

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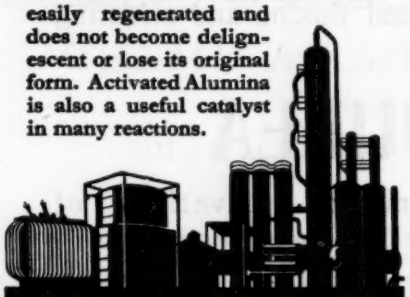

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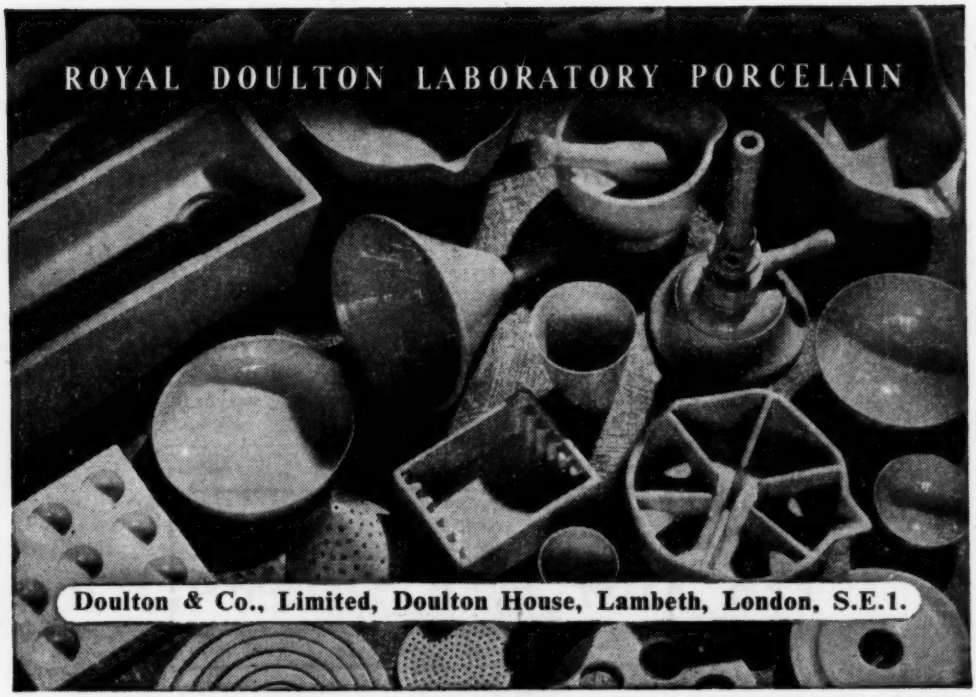

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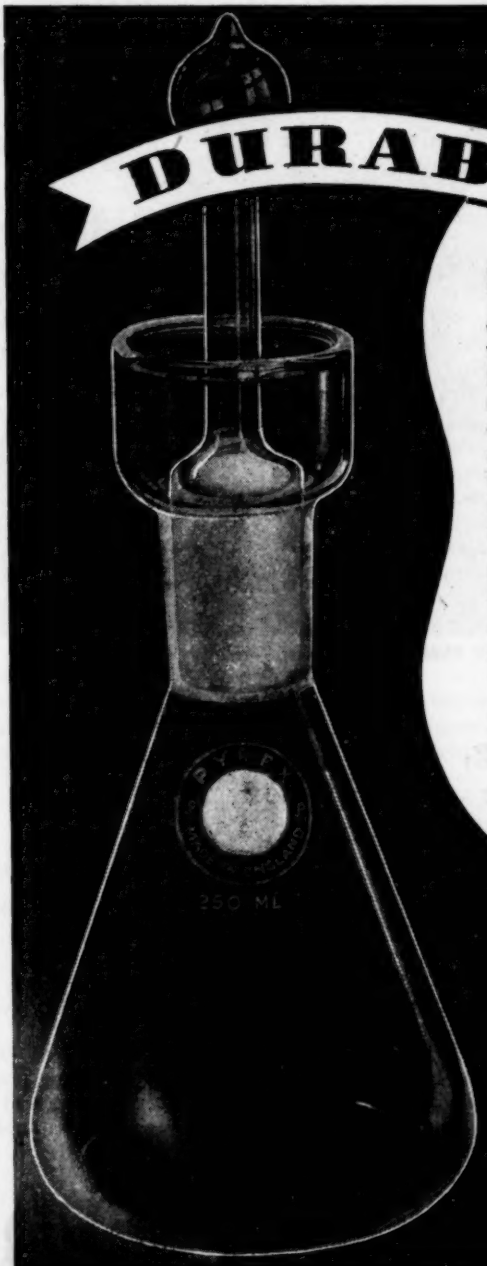

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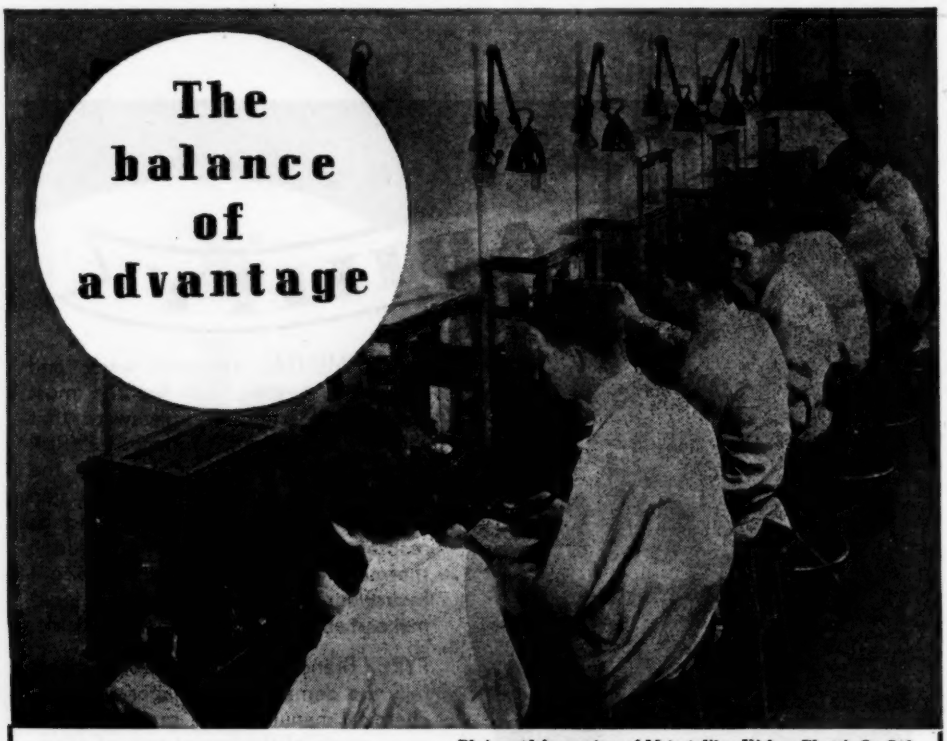

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the problem of the mechanism of autoxidation and polymerisation of drying oils, particularly tung oil, from which he prepared derivatives in pure form suitable for experimental study. He stressed continually the differences in reactivity of the three double bonds of the elæostearic acid molecule and finally cleared the ground with the different maleic anhydride adducts of α- and β-elæostearic acid, which he isolated and characterised; he concluded that in the α-compound the double bond near to the carboxyl group remained free, and in the β-compound, the bond remote from the carboxyl. These adducts prepared by Morrell were used by Rideal for the first studies of the autoxidation of drying oils by the surface film technique.

Three text books which he wrote " Varnishes and their Components ", " The Chemistry of Drying Oils " (with H. R. Wood), and " Rubber, Resins, Paints & Varnishes " (with A. de Waele) are still standard works, and it should not be forgotten that they were produced at a time when such books were scarce. More recently, he edited " The Chemistry of Natural and Synthetic Resins " and " Synthetic Resins and Allied Plastics ".

Morrell took a wide interest in art and artists and lectured on the Chemistry of Artists' Materials in London over the period 1931—1937; these lectures were published in book form in 1939. He also contributed the section upon Drying Oils for the *Annual Reports on the Progress of Applied Chemistry*.

Morrell was a prominent figure in the early days of the Oil and Colour Chemists' Association and was President during 1920 and 1921, in which office he succeeded Mollwo Perkin.

During the period 1920—1926, Morrell lent all his aid to the thesis that the obviously developing need of research in the paint and varnish industry must be met; when the Research Association of British Paint, Colour and Varnish Manufacturers was formed in 1926 he was a staunch supporter and gave freely of his knowledge and experience as a member of Council.

Throughout his life Morrell was an enthusiastic worker in what would be now called " further education ". In his Cambridge days he lectured under the auspices of the Kent County Council and later for the Workers' Educational Association. For many years he and his wife, who died in July 1946, served the Wolverhampton centre of the Oxford University Extension Lectures as treasurer and secretary respectively.

He was a President of the Wolverhampton branch of the Historical Association, a member for 25 years of the Wolverhampton Rotary Club, and a co-opted member of the Corporation Art Gallery and Public Library Committee.

He was a staunch Churchman and a greatly admired and loved member of the community of Tettenhall Wood where he lived for thirty-five years. His friends and associates in a wider field also remember him as a rich and lovable personality who used his gifts freely and unsparingly in the service of all who called upon him.

L. A. JORDAN.

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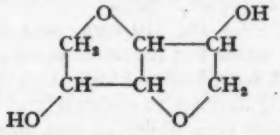
86. *Anhydrides of Polyhydric Alcohols. Part VI.* 1 : 4-3 : 6-*Dianhydro Mannitol and* 1 : 4-3 : 6-*Dianhydro Sorbitol from Sucrose.*

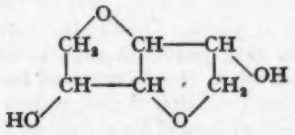
By R. MONTGOMERY and L. F. WIGGINS.

Details of methods of production of 1 : 4-3 : 6-dianhydro mannitol and 1 : 4-3 : 6-dianhydro sorbitol in pure crystalline form from sucrose are given.

THE dianhydrides of mannitol and sorbitol, known as *iso*mannide and *iso*sorbide respectively, can be prepared from the respective hexahydric alcohols by treatment with acid reagents. Both these compounds have been shown to possess the 1 : 4-3 : 6-ring structure by Wiggins (*J.*, 1945, 4) and Montgomery and Wiggins (*J.*, 1946, 390), so dianhydro sorbitol is represented by (I) and dianhydro mannitol by (II).



(I.)



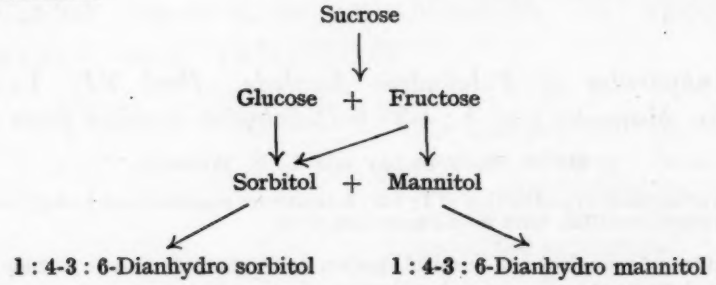
(II.)

These substances are becoming of some interest to chemists, from both the industrial and the academic viewpoint. They have already proved of interest in the former aspect since it has been possible to prepare excellent drying oils from them by condensation with certain

unsaturated carboxylic acids, and also wetting agents by condensation with saturated fatty acids. Moreover, recent patents have been granted to the Atlas Powder Company for resinous products derived from these compounds. We have prepared a number of derivatives of these dianhydrides. The 2 : 5-diamino-derivatives give rise to sulphanilamido-derivatives which, however, possess no outstanding chemotherapeutic properties (Montgomery and Wiggins, *J.*, 1946, 393). Krantz (U.S.P., 2,143,324, 1939) found that dianhydro mannitol was a diuretic agent and that the dinitrates of both dianhydrides are useful in the treatment of angina pectoris and other hypertension conditions (Krantz, Carr, Forman, and Ellis, *J. Pharm.*, 1939, **67**, 191), though we have found that the dinitrate of dianhydro sorbitol possesses twice the activity of the corresponding derivative of dianhydro mannitol. The acrylate and methacrylate of dianhydro mannitol and dianhydro sorbitol (Haworth, Gregory, and Wiggins, *J.*, 1946, 488) are of interest since they polymerise very easily without catalysts to hard transparent resins and copolymerise homogeneously with methyl methacrylate. Also the 2 : 5-diallyl and 2 : 5-dicrotyl ethers may be valuable as solvents of the plasticizer class (patent applied for).

Since we have been concerned with the development of the chemistry of sucrose to increase its use in industry, it occurred to us that the conversion of sucrose into these dianhydro compounds would help this project.

It is known that sucrose or invert sugar is reduced to a mixture of mannitol and sorbitol by means of catalytic hydrogenation, or, in the case of invert sugar, by electrolytic reduction. We have carried out experiments in order to find the optimum conditions for reducing sucrose and invert sugar under high temperature–high pressure hydrogenating conditions in the presence of Raney nickel catalyst. A theoretical yield of mannitol and sorbitol was obtained by hydrogenating an aqueous solution of sucrose at 160° provided that this working temperature was attained slowly. The necessity for slow heating is due to the fact that the heating of sucrose with water at 135—140° results in the development of acid conditions (pH 3·10), a change which is accompanied by inversion of the sucrose to glucose and fructose (Montgomery and Wiggins, *J. Soc. Chem. Ind.*, 1947, **65**, 31) and a further degradation at slightly higher temperatures (160°) with the formation of 5-hydroxymethyl-2-furfuraldehyde, lævulic acid, formic acid, and humin substances, of which the last tends to deactivate the catalyst. A slow rate of heating in the hydrogenation reaction therefore ensures complete reduction of the glucose and fructose as they are formed and eliminates the degradation reactions. A quantitative yield of the mixture of mannitol and sorbitol from invert sugar was obtained by hydrogenation in the presence of Raney nickel at 120° and 100 atm. pressure in a weakly alkaline buffered solution. It was essential in this case to keep the working temperature below 125°, particularly in the earlier stages of the reduction.



The dianhydrides of mannitol and sorbitol were obtained in the initial experiments by heating the above mixture of mannitol and sorbitol with hydrochloric acid under reflux for 75—95 hours. The syrupy product from this treatment was fractionally distilled; pure dianhydro mannitol distilled first at 136—140°/10 mm. and was obtained crystalline in 30% of the theoretical yield. Dianhydro sorbitol distilled at 160—165°/10 mm. and was obtained crystalline in 59% yield. A slightly better yield of the latter but a poorer yield of the former was obtained when the mixture of hexitols was heated with hydrochloric acid for 12 hours, followed by fractionation of the product, which was mainly dianhydro sorbitol, and re-treatment of the residues with acid for a further 72 hours; there were then obtained further quantities of both dianhydro compounds. In this way crystalline dianhydro sorbitol was obtained in 62% and dianhydro mannitol in 10% of the theoretical yield. The essential scheme for the production of the two dianhydrides from sucrose is shown in the diagram. An investigation has been carried out on the action of acid catalysts other than hydrochloric acid on pure mannitol and

sorbitol obtained by fractional recrystallisation of the hexitol mixture from the hydrogenation of sucrose or invert sugar. In general, the experimental procedure consisted of suspending the hexitol in an inert solvent and heating the mixture in the presence of an acid catalyst. The experiments were first carried out so that the water produced in the reaction was azeotropically removed by slow distillation with an entraining liquid (usually xylene) in a vigorous stream of nitrogen. A second experimental procedure involved heating the mixture under reflux with xylene accompanied by vigorous mechanical stirring.

The acids chosen to act as catalysts were *p*-toluenesulphonic, concentrated sulphuric, and phosphoric. The proportion of acid to hexitol was varied, as was the time of the reaction, in order to determine the conditions for each acid at which the maximum yield of dianhydro mannitol and dianhydro sorbitol was obtainable. The results are summarised in the table for *p*-toluenesulphonic and sulphuric acid, but the use of phosphoric acid as a catalyst did not seem to be satisfactory owing to the formation of phosphoric esters, a phenomenon which had been observed by Carré (*Ann. Chim. Phys.*, 1905, **5**, 429), and the recovery of much unchanged hexitol.

It is noteworthy that dianhydro mannitol was never isolated in more than about 30% yield, and this has been found to be due to the additional formation of different anhydro compounds (Montgomery and Wiggins, unpublished work).

Hexitol, and wt. (g.).	Acid catalyst, and wt. (g.).	Reaction temp.	Time (hrs.).	Procedure.	Yield of dianhydride (%).
Mannitol 30	Conc. H_2SO_4 2·0	130—140°	1½	1	16·0
,, 50	,, 4·0	,,	,,	,,	26·6
,, 30	,, 4·0	,,	2½	,,	29·6
,, 30	,, 2·0	,,	,,	,,	31·2
Sorbitol 30	,, 2·0	,,	1¼	,,	67·0
,, 30	,, 2·8	,,	,,	,,	64·5
,, 30	,, 4·0	130—160	2½	,,	61·0
Mannitol 30	*p*-C_7H_7·SO_3H 2·0	130—135	2½	,,	8·3
,, 30	,, 2·0	150—155	1¼	,,	25·4
,, 30	,, 10·5	140—144	4	2	24·2
,, 30	,, 10·5	,,	1	,,	26·2
Sorbitol 20	,, 1·2	,,	1¼	,,	28·1
,, 20	,, 1·2	,,	4	,,	29·4
,, 20	,, 3·7	,,	,,	,,	48·0
,, 20	,, 7·0	,,	,,	,,	61·0

Experimental.

Hydrogenation of Sucrose.—Sucrose (100 g.), dissolved in water (500 c.c.), was hydrogenated at 160° under 100 atm. for 6 hours with Raney nickel catalyst. The reaction mixture was initially heated as rapidly as possible until the temperature was 100°, and the rate of heating was then reduced so that the working temperature was not reached until 2 hours from the commencement of the heating. The resulting mixture was filtered and evaporated to dryness. A theoretical yield of crystalline mannitol and sorbitol was obtained.

Preparation of Invert Sugar Solution.—Sucrose (500 g.) was slowly added to continuously stirred, boiling 0·1N-sulphuric acid (1900 c.c.), and the solution kept boiling for one minute after the sucrose had been added; it was then allowed to cool for one hour, after which it was neutralised with a hot aqueous solution of barium hydroxide octahydrate (32 g.), and the precipitated barium sulphate removed by centrifuging.

Hydrogenation of Invert Sugar Solution.—To the above solution of invert sugar were added anhydrous sodium carbonate (2·0 g.), calcium carbonate (80 g.), and Raney nickel catalyst (8—9 g.), and the mixture was hydrogenated at 110—120° under 75—100 atm. for 6½—7 hours. After cooling, the resulting mixture was filtered, and the filtrate evaporated to dryness. A theoretical yield of hexitols was obtained.

Preparation of Dianhydro Mannitol and Dianhydro Sorbitol from a Mixture of Mannitol and Sorbitol.—(1) A mixture of mannitol and sorbitol (500 g.) obtained from either of the above hydrogenation reactions was heated under reflux with concentrated hydrochloric acid (2 l.) for 12 hours. The resulting solution was concentrated under reduced pressure, and the residue distilled under 12 mm. pressure, the distillate (142 g.) being collected between 125° and 225° (bath temp.). The distillate was fractionally distilled, yielding dianhydro mannitol (3·0 g.) and dianhydro sorbitol (106·1 g.). The residues from these distillations were re-treated for 3 days with boiling concentrated hydrochloric acid (2 l.), and the dianhydro mannitol (12·1 g.) and dianhydro sorbitol (80·4 g.) separated as above. Again all the residues were retreated for 3 days with concentrated hydrochloric acid (1 l.) and yielded dianhydro sorbitol (11·0 g.) and an unidentified high-boiling liquid (48·7 g.), b. p. 145°/0·01 mm. The final yields, after recrystallisation of both compounds from ethyl acetate, were: dianhydro mannitol, 15·1 g. (9·5%), m. p. 85—87°, b. p. 136—140°/10 mm.; dianhydro sorbitol, 143·0 g. (62·0%), m. p. 57—61°, b. p. 160—165°/10 mm.

(2) A mixture of mannitol and sorbitol (500 g.), obtained from the hydrogenation of invert sugar (500 g.), was heated under reflux with concentrated hydrochloric acid (2 l.) for 4 days. The resulting solution was evaporated, and the residue fractionally distilled to yield dianhydro mannitol and dianhydro

sorbitol. Both compounds were recrystallised from ethyl acetate, the final yields being 40 g. (30%) and 162 g. (59%), respectively.

Action of Concentrated Hydrochloric Acid on Mannitol.—Mannitol (30 g.) was refluxed for one hour with concentrated hydrochloric acid (120 c.c.), and the resulting solution evaporated to dryness under reduced pressure. The crystalline residue was treated with boiling ethyl alcohol (30 c.c.), cooled, and filtered, the unchanged mannitol (29 g.) being recovered in this way. The ethyl-alcoholic solution was evaporated, and the residue heated at 200° (bath temp.) under reduced pressure for 2 hours, during which no material distilled.

The above experiment was repeated with the exception that the heating was continued for 3½ days. The products from 1000 g. of mannitol were dianhydro mannitol (193 g.) and a mixture of other anhydro derivatives (144·3 g.).

Action of Concentrated Hydrochloric Acid on Sorbitol.—Sorbitol (30 g.) was refluxed with concentrated hydrochloric acid (120 c.c.) for one hour, and the resulting solution evaporated to dryness under reduced pressure. The syrupy residue was heated at 200—230° (bath temp.)/12 mm. until no more material distilled. The distillate (9·2 g.) rapidly crystallised, and recrystallised to give dianhydro sorbitol, m. p. 60—61° (8·4 g., 35%).

Repetition of the above experiment with 500 g. of sorbitol, with the exception that the heating was continued for 24 hours, yielded dianhydro sorbitol (265 g., 66%).

Dehydration of Mannitol or Sorbitol with Acid Catalysts.—The hexitol, suspended in dry xylene, was heated in the presence of sulphuric, *p*-toluenesulphonic, or phosphoric acid according to one of the procedures given below.

Procedure 1. The reaction mixture was heated at the required temperature in a vigorous stream of nitrogen. At the end of the heating, the mixture was cooled, the xylene decanted off, and the syrupy residue dissolved in aqueous alcohol, neutralised with sodium carbonate, and filtered. The filtrate was evaporated to dryness, and the residue distilled under reduced pressure. Recrystallisation of the distillate from ethyl acetate yielded the pure dianhydro compound.

Procedure 2. The reaction mixture, suspended in xylene, was heated under reflux with vigorous mechanical stirring and the product was then treated exactly as described in Procedure 1.

The results are seen in the table.

The authors are grateful to Professors W. N. Haworth, F.R.S., and J. L. Simonsen, F.R.S., for their interest and encouragement, and to the Colonial Products Research Council for financial assistance.

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM, 15. [*Received, July 15th*, 1946.]

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87. *The Action of Grignard Reagents on Esters of Optically Active Carboxylic Acids.*

By A. CAMPBELL and J. KENYON.

When methylmagnesium iodide and phenylmagnesium bromide react with (−)methyl hydratropate, the resulting tertiary alcohols are optically active.

Two different suggestions have been advanced as to the course of the reaction which occurs when a tertiary alcohol is produced by the interaction of a Grignard reagent and a carboxylic ester (Grignard, *Compt. rend.*, 1901, **132**, 336; Boyd and Hatt, *J.*, 1927, 898), but they have this in common—they both restrict the reactivity of the ester to the $\cdot CO_2R$ part of the molecule $R' \cdot CO_2R$.

It follows from this view of the mechanism of the reaction that when the reacting ester is derived from an optically active carboxylic acid the resulting tertiary alcohol will itself be optically active since the four bonds of the asymmetric atom present in the radical R′ remain undisturbed.

On the other hand it is stated by Bergmann and Hartrott (*J.*, 1935, 1218) that when the methyl ester of (−)-1-methylbutane-1-carboxylic acid reacts with phenylmagnesium bromide the resulting 1 : 1-diphenyl-2-methylpentan-1-ol is optically inactive. The authors recognise that this result is unexpected and to account for it they put forward several suggestions, one of which is that " the carbinol (or its bromomagnesium derivative) when formed undergoes spontaneously reversible dehydration $CHMePr \cdot CPh_2 \cdot OH \rightleftharpoons CMePr{:}CPh_2$ which must be accompanied by racemisation ".

Although we considered this explanation inherently improbable we decided to investigate the reaction in case it could throw light on the failure of attempts to resolve racemic tertiary alcohols by the hydrogen phthalic ester procedure which has proved successful for the resolution of the less easily dehydrated secondary alcohols. (−)Methyl hydratropate reacts readily with methylmagnesium iodide and with phenylmagnesium bromide to yield the corresponding tertiary alcohols, both of which are optically active.

If Bergmann and Hartrott (*loc. cit.*) are right in supposing that tertiary alcohols which

contain two phenyl radicals are capable of undergoing reversible dehydration when produced in the presence of excess of a Grignard reagent and subsequently of isolation as virtually pure alcohols, it seems reasonable to suppose that the equilibrium may be approached from the other side, and that the ethylenic dehydration product dissolved in the same excess of a Grignard reagent should, on addition of a molecular proportion of water, yield the virtually pure alcohol.

To test this hypothesis 1 : 1 : 2-*triphenylpropylene*, dissolved in four molecular proportions of phenylmagnesium bromide, was mixed with one molecular proportion of water : the mixture was then heated under reflux for two hours and decomposed in the usual manner, but no trace of tertiary alcohol was found and the unsaturated hydrocarbon was recovered unchanged.

It seems unlikely therefore that the optically active ester used by these authors underwent racemisation as a result of the reaction they describe. It may have been racemised by some undescribed agency : the ready racemisation of carboxylic esters under alkaline conditions (cf. Kenyon and Young, *J.*, 1940, 216) may be noted in this connexion.

Experimental.

(−) + *dl*-Methyl hydratropate, prepared from incompletely resolved hydratropic acid [15 g. of α_{5461} − 21·45° (*l*, 0·5)] (yield, 14 g.), had b. p. 109—110°/14 mm.; $d_4^{18°}$ 1·0353; $n_D^{18°}$ 1·5008; α_{5893}^{20} − 19·28°, $\alpha_{5461}^{20°}$ − 23·55° (*l*, 0·5).

(+) + *dl*-1 : 1-*Dimethyl*-2-*phenylpropan*-1-*ol*.—The methyl hydratropate (5 g.) was added dropwise to a solution of methylmagnesium iodide (Mg, 3 g.; MeI, 17·5 g.) and the mixture, after being heated under reflux for 2 hours, was decomposed with ammonium chloride solution. The resulting tertiary *alcohol*, b. p. 135—136°/15 mm. (yield, 5 g.), had $d_4^{20°}$ 1·0372; $n_D^{22°}$ 1·5162; $\alpha_{5893}^{20°}$ + 3·44°, $\alpha_{5461}^{20°}$ + 4·02° (*l*, 0·5) (Found : C, 80·3; H, 9·9. $C_{11}H_{16}O$ requires C, 80·5; H, 9·7%).

(+) + *dl*-1 : 1 : 2-*Triphenylpropan*-1-*ol*.—Prepared as described above from the methyl ester (5 g.) and Grignard reagent (Mg, 3·2 g.; PhBr, 23·4 g.), this *alcohol* had b. p. 180—183°/15 mm. (yield 4 g.), and formed prisms from light petroleum, m. p. 90°; $[\alpha]_{5893}$ + 35°, $[\alpha]_{5461}$ +49° (*l*, 0·5; *c*, 2·40 in methanol); $[\alpha]_{5893}$ + 34°, $[\alpha]_{5461}$ + 53 (*l*, 0·5; *c*, 2·10 in chloroform) (Found : C, 87·5; H, 6·7. $C_{21}H_{20}O$ requires C, 87·5; H, 6·9%).

1 : 1 : 2-*Triphenylpropylene*.—A solution of 1 : 1 : 2-triphenylpropanol (10 g.) and iodine (0·1 g.) in benzene (10 c.c.) was heated under reflux for 24 hours, washed with sodium thiosulphate solution, and dried. The resulting *triphenylpropylene* had b. p. 174—177°/15 mm. (yield 7 g.) and separated from light petroleum in prisms, m. p. 93° (Found : C, 93·6; H, 6·8. $C_{21}H_{18}$ requires C, 93·3; H, 6·7%).

Attempted Hydration of 1 : 1 : 2-*Triphenylpropylene*.—The hydrocarbon (5 g.) was added to phenylmagnesium bromide (4 mols.); no visible reaction occurred. Water (0·3 c.c.) was then added dropwise to the stirred solution and the whole heated under reflux for 2 hours. Decomposition of the reaction mixture in the usual manner yielded unchanged 1 : 1 : 2-triphenylpropylene (4·5 g.), m. p. 93°, alone and when mixed with the untreated material.

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88. *The Skraup Reaction with* m-*Substituted Anilines.*

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A number of 5- and 7-substituted quinoline derivatives have been unambiguously synthesised and used to identify the products of the Skraup reaction with *m*-substituted anilines. The modified Skraup reaction of B.P. 394,416 (I.G. Farbenindustrie A.-G.) has been applied to *m*-nitroaniline, *m*-toluidine, *m*-aminobenzoic acid, *m*-aminodimethylaniline, *m*-chloroaniline, *m*-bromoaniline, *m*-aminophenol, *m*-anisidine, and metanilic acid, and variations of the yield and of the ratio in which the isomers occur have been investigated. There is a relation between the nature of the *m*-substituent group in the aniline employed and the ratio of isomers obtained.

The Skraup reaction with *m*-substituted anilines in which both positions *o*- to the amino-group are free can give rise to either the 5- or the 7-substituted quinoline :

and, in general, the formation of a mixture of the two isomers would be anticipated. Information in the literature is often incomplete; in some cases only one isomer is recorded, whilst in others the relative proportions of the isomers have not been investigated. The modified Skraup reaction of B.P. 394,416 (I.G. Farbenindustrie A.-G.), using 60—80% aqueous sulphuric acid, is claimed to eliminate the normal violence of a Skraup reaction and to give products free

from tars in good yield, thus lending itself to more accurate investigation of the composition of the mixture obtained from a *m*-substituted aniline. The literature indicated that the orientation of 5- and 7-substituted quinolines in general was unsatisfactory, and we have now orientated the derivatives liable to be formed in the Skraup reaction from a number of *m*-substituted anilines.

4-Nitro-2-aminobenzoic acid was converted by a Skraup reaction into 5-nitroquinoline-8-carboxylic acid, which was then decarboxylated to give 5-nitroquinoline. This was reduced to 5-aminoquinoline which was converted *via* diazotisation into 5-chloroquinoline, identical in properties with the substance described as 7-chloroquinoline by Claus and Kayser (*J. pr. Chem.*, 1893, **48**, 270). The conclusion reached by Fourneau, Trefouel, and Wancolle (*Bull. Soc. chim.*, 1930, **47**, 738) that the substance so described is actually the 5-isomer is thus confirmed. 5-Bromo- and 5-cyano-quinoline were also obtained similarly. The existence of a so-called "*pseudo*-5-cyanoquinoline" in addition to 5-cyanoquinoline (Lellmann and Reusch, *Ber.*, 1888, **21**, 397) was disproved. Hydrolysis of 5-cyanoquinoline gave quinoline-5-carboxylic acid, identical in properties with the "*pseudo*quinoline-5-carboxylic acid" described by Lellmann and Alt (*Annalen*, 1887, **237**, 307). Consequently, the characteristics recorded by Schlosser and Skraup (*Monatsh.*, 1881, **2**, 518) for quinoline-5-carboxylic acid are incorrect. 5-Hydroxyquinoline was obtained from 5-aminoquinoline. Owing to the discrepancy in recorded b. p. of 5-methylquinoline, the synthesis of Jakubowski (*Ber.*, 1910, **43**, 3026) was repeated. 5-*Methoxyquinoline* also was synthesised in an analogous manner.

In an attempt to synthesise 7-chloroquinoline, 7-*chloro*-8-*methylquinoline* was obtained, but this could not be oxidised to 7-chloroquinoline-8-carboxylic acid. The synthesis of a 7-substituted quinoline derivative was finally achieved by preparing 7-methylquinoline from 2 : 3-diaminotoluene by converting it into 8-*amino*-7-*methylquinoline* and eliminating the amino-group from the latter. 7-Methylquinoline was oxidised to quinoline-7-carboxylic acid, and the latter formed a basis for the orientation of the second nitroquinoline obtained as a product of the Skraup reaction with *m*-nitroaniline. This nitroquinoline was converted, *via* an amino- and a cyano-quinoline, into a carboxylic acid identical with quinoline-7-carboxylic acid, thus confirming that these compounds are 7-nitro-, 7-amino-, and 7-*cyano-quinoline*, respectively. 7-Chloroquinoline was obtained from 7-aminoquinoline *via* the diazo-compound and possessed properties which agreed with those described by Claus and Junghanns (*J. pr. Chem.*, 1893, **48**, 253) for 5-chloroquinoline. Obviously these authors, together with Claus and Kayser (*loc. cit.*), confused the orientation of the two isomers. 7-Bromo- and 7-hydroxyquinoline were also obtained from 7-aminoquinoline. The halogen atom in both 7-chloro- and 7-bromo-quinoline proved to be sufficiently labile to be partially replaced by heating with aqueous dimethylamine under pressure to give 7-*dimethylaminoquinoline*. 7-Bromoquinoline was also converted into 7-methoxyquinoline by heating with sodium methoxide under pressure, but attempts to obtain amino- and hydroxy-compounds by analogous methods were unsuccessful.

The Skraup reaction with *m*-nitroaniline gave a mixture of 5- and 7-nitroquinolines in the ratio of 3·5 : 1. Experiments were carried out with 63% to 90% sulphuric acid, the reaction only becoming violent with concentrated acid. The isomers were separated by crystallising 5-nitroquinoline nitrate, followed by basifying and refluxing the residual mixture with ligroin. The use of sodium *m*-nitrobenzenesulphonate as oxidising agent in place of arsenic acid had little effect on the yield of 7-nitroquinoline, but considerably reduced the yield of 5-nitroquinoline.

The product of the Skraup reaction with *m*-toluidine was solely 7-methylquinoline identical with a synthetic specimen, and the reaction proceeded smoothly except with the highest concentration of sulphuric acid used.

The Skraup reaction with *m*-aminobenzoic acid gave a mixture of quinoline-5- and -7-carboxylic acids in the ratio of 5 : 1, whereas the formation of quinoline-5-carboxylic acid only has been recorded in the literature. The isomers were separated by means of their different acidities.

The Skraup reaction with *m*-aminodimethylaniline has only been previously described by Knüppel (*Ber.*, 1896, **29**, 703), who assumed the product to be 7-dimethylaminoquinoline, but recorded no characteristics. The yield obtained from *m*-aminodimethylaniline is low because it is easily oxidisable, but both 7- and 5-*dimethylaminoquinoline* were formed in the ratio of approximately 7 : 1.

The Skraup reaction with *m*-chloroaniline gave a mixture of 5- and 7-chloroquinolines (cf. La Coste, *Ber.*, 1885, **18**, 2940) which was separated by fractional crystallisation of the dichromates (Claus and Junghanns, *loc. cit.*); the perchlorates, oxalates, nitrates, or picrates

could not be utilised satisfactorily for this purpose. The ratio of the isomers obtained depended upon the concentration of sulphuric acid used in the Skraup reaction, but was independent of the time of reaction at any acid concentration examined. When 60% sulphuric acid was used, the ratio of 7- to 5-chloroquinoline was 1·4 : 1, rising gradually to 4·4 : 1 as the concentration of the sulphuric acid was increased to 85%.

The Skraup reaction with *m*-bromoaniline gave a mixture of 5- and 7-bromoquinolines (Claus and Tornier, *Ber.*, 1887, **20**, 2872) which was also separated by fractional crystallisation of the dichromates, but in this case the two isomers were formed in approximately equal proportion under all the conditions examined.

The Skraup reaction with *m*-aminophenol gave 7-hydroxyquinoline as sole product in moderate yield, although the m. p. of the picrate indicated that a little 5-hydroxyquinoline may be formed when low concentrations of sulphuric acid are used.

The Skraup reaction with *m*-anisidine using 65% to 75% sulphuric acid gave in low yield a product identical with synthetic 7-methoxyquinoline.

The Skraup reaction with metanilic acid using nitrobenzene as oxidising agent gave a mixture of quinoline-5- and -7-sulphonic acids (Lellmann and Lange, *Ber.*, 1887, **20**, 1446, referred to the presence of only the 5-sulphonic acid). Owing to difficulty in purifying the product, it was not found possible to use *m*-nitrobenzenesulphonic acid, its sodium salt, or arsenic acid as oxidising agent. The presence of both isomers was established by a cyanide fusion, followed by hydrolysis to the corresponding carboxylic acids, from which both quinoline-5- and -7-carboxylic acids were separated. In order to form a basis for the quantitative separation of the sulphonic acids many attempts were made to obtain suitable derivatives with m. ps. but none was successful; the chloride, ethyl ester, amide, anilide, methylanilide, arylamine salts, and *S*-benzylthiouronium salt could not be prepared. The following conclusions may be drawn from the results of examining the Skraup reaction under the conditions of B.P. 394,416 with nine *m*-substituted anilines :

(*a*) Strongly *o*-*p*-directing groups, *e.g.*, methyl, hydroxyl, and methoxyl groups, give only the 7-substituted quinoline.

(*b*) Relatively weaker *o*-*p*-directing groups, *e.g.*, chloro-, bromo-, and dimethylamino-groups, give a mixture of 5- and 7-substituted quinolines, in which the latter predominates.

(*c*) *m*-Directing groups, *e.g.*, nitro-, carboxyl, and sulphonic groups, give a mixture of 5- and 7-substituted quinolines, in which the former predominates.

(*d*) In only one case, *viz.*, *m*-chloroaniline, was the ratio of the isomers obtained found to be influenced by the concentration of the sulphuric acid used in the Skraup reaction.

Experimental.

Orientation of 5-Substituted Quinoline Derivatives.

5-Nitroquinoline.—4-Nitro-2-aminobenzoic acid (25 g.) (Wheeler and Johns, *Amer. Chem. J.*, 1910, **44**, 443), sulphuric acid (65%; 350 g.), glycerol (50 g.), and arsenic acid (80% w./w.; 125 g.) were refluxed with stirring for 4 hours; the temperature fell from 137° to 133°. The solution was diluted to 2 l., made alkaline with sodium hydroxide solution, and then acidified with acetic acid. The pale brown precipitate (21 g.), containing inorganic matter, was crystallised from alcohol to give colourless minute prisms, m. p. 215° (Howitz and Nöther, *Ber.*, 1906, **39**, 2705, give m. p. 212°) (Found : C, 55·3; H, 3·0; N, 12·2. Calc. for $C_{10}H_6O_4N_2$: C, 55·0; H, 2·75; N, 12·8%). 5-Nitroquinoline-8-carboxylic acid (4 g.) was converted into the silver salt and heated in a vacuum to give 5-nitroquinoline, which crystallised from aqueous alcohol (charcoal) in colourless plates, m. p. 70° (0·5 g.; 16%) (Found : C, 61·2; H, 3·5; N, 15·5. Calc. for $C_9H_6O_2N_2$: C, 62·1; H, 3·45; N, 16·1%). The nitrate crystallised from water in pale yellow minute prisms, m. p. 195°.

5-Aminoquinoline.—5-Nitroquinoline was reduced to 5-aminoquinoline by the method of Kochanska and Brobanski (*Ber.*, 1936, **69**, 1807). It crystallised from alcohol in yellow needles, m. p. 106° (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 147, gives m. p. 110°) (Found : C, 74·6; H, 5·3; N, 20·2. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·55; N, 19·5%); hydrochloride, colourless crystals, m. p. 259° (decomp.); the acetyl derivative crystallised from aqueous alcohol in colourless microscopic needles, m. p. 181° (Hamer, *J.*, 1921, **119**, 1436, gives m. p. 178°).

5-Cyanoquinoline.—5-Aminoquinoline was converted into 5-cyanoquinoline by the method of Freydl (*Monatsh.*, 1887, **8**, 580). After crystallising from ligroin in colourless minute plates and drying in a desiccator, it had m. p. 88° (Freydl gives m. p. 87°) (Found : C, 77·8; H, 4·0; N, 17·5. Calc. for $C_{10}H_6N_2$: C, 77·9; H, 3·9; N, 18·2%). After recrystallising from dilute alcohol and drying for 10 minutes on a porous plate, a hydrate, m. p. 70°, was obtained (cf. Lellmann and Reusch, *Ber.*, 1888, **21**, 397). It formed a yellow *picrate*, almost insoluble in alcohol, m. p. 241° (Found : C, 50·3; H, 2·5. $C_{10}H_6N_2,C_6H_3O_7N_3$ requires C, 50·1; H, 2·35%); a yellow *styphnate*, almost insoluble in alcohol, m. p. 241° (decomp.) (Found : C, 48·1; H, 2·6. $C_{10}H_6N_2,C_6H_3O_8N_3$ requires C, 48·1; H, 2·25%); a *nitrate*, which crystallised from water in colourless prisms, m. p. 219° (Found : C, 55·2; H, 3·2. $C_{10}H_6N_2,HNO_3$ requires C, 55·3; H, 3·2%); and a *hydrochloride*, colourless prisms, m. p. 248° (Found : Cl, 18·3. $C_{10}H_6N_2,HCl$ requires Cl, 18·6%).

Quinoline-5-carboxylic Acid.—5-Cyanoquinoline was refluxed with 60% sulphuric acid; the quinoline-5-carboxylic acid separated from glacial acetic acid–alcohol in colourless crystals, m. p. 342° (Lellmann and Alt, *Annalen*, 1887, **237**, 307, give m. p. 338°) (Found: C, 68·9; H, 4·15; N, 7·9. Calc. for $C_{10}H_7O_2N$: C, 69·3; H, 4·1; N, 8·1%). It was reduced by the method of Fischer and Körner (*Ber.*, 1884, **17**, 765) to 1 : 2 : 3 : 4-tetrahydroquinoline-5-carboxylic acid, colourless needles, m. p. 147°.

5-Chloroquinoline.—5-Aminoquinoline (6 g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and water (25 c.c.) and the solution diazotised at 0° by adding sodium nitrite (5 g.) in water. The diazo-solution was poured into a cooled solution of cuprous chloride (4 g.) in hydrochloric acid (30%; 30 c.c.) and, after 5 minutes, the mixture was heated on the steam-bath for 30 minutes. After the mixture had been made alkaline with sodium hydroxide, the 5-chloroquinoline was distilled with steam and extracted from the distillate with ether. It crystallised from ether in colourless needles, m. p. 43°, b. p. 256—257°/756 mm. (4 g.; 59%) (Found: C, 65·9; H, 3·9; N, 8·1. Calc. for C_9H_6NCl: C, 66·1; H, 3·7; N, 8·6%); the dichromate formed orange microscopic needles, m. p. 121° (decomp.); the *nitrate*, colourless prismatic needles from water, m. p. 159—161° (Found: N, 12·0. C_9H_6NCl,HNO_3 requires N, 12·4%); the oxalate, colourless needles, m. p. 145°; the *perchlorate*, colourless microscopic needles from aqueous alcohol, m. p. 198° (Found: C, 41·3; H, 2·8. $C_9H_6NCl,HClO_4$ requires C, 40·9; H, 2·65%).

5-Bromoquinoline.—5-Aminoquinoline (10 g.) was dissolved in hydrobromic acid (40%; 25 c.c.) and water (250 c.c.), and diazotised at 0° with sodium nitrite (5 g.) in water. Cuprous bromide (12 g.) was dissolved in hydrobromic acid (40%; 40 c.c.) and water, and the diazo-solution was added to this solution. The mixture was heated on the steam-bath for 30 minutes, made alkaline with sodium hydroxide, and distilled with steam, and the 5-bromoquinoline was extracted from the distillate with ether. It crystallised from ether in colourless needles, m. p. 46—48°, b. p. 280°/756 mm. (7 g.; 48%); the *dichromate* formed deep-yellow needles from water, m. p. 134° (decomp.) (Found: C, 33·8; H, 2·7. $(C_9H_6NBr)_2,H_2Cr_2O_7$ requires C, 34·1; H, 3·1%); the nitrate, colourless needles, m. p. 193° (decomp.) (Claus and Vis, *J. pr. Chem.*, 1888, **38**, 387, give m. p. 185°); the oxalate, colourless needles, m. p. 152°; the *picrate*, insoluble in alcohol, m. p. 235° (Found: N, 12·4. $C_9H_6NBr,C_6H_3O_7N_3$ requires N, 12·8%).

5-Hydroxyquinoline.—5-Aminoquinoline (5 g.) was converted into 5-hydroxyquinoline (cf. Kochanska and Brobanski, *loc. cit.*), buff-coloured leaflets, m. p. 224° (1 g.; 20%). It formed a hydrochloride, dark-coloured prisms, m. p. 242°; a *picrate*, which crystallised from alcohol in long orange-yellow needles, m. p. 187° (Found: N, 14·7. $C_9H_7ON,C_6H_3O_7N_3$ requires N, 14·95%); and an *oxalate*, buff-coloured microscopic needles from alcohol, m. p. 193° [Found: C, 64·3; H, 3·9. $(C_9H_7ON)_2,(CO_2H)_2$ requires C, 64·6; H, 4·2%].

5-Methylquinoline.—*m*-Amino-*p*-tolyl cyanide (20 g.) (von Niementowski, *J. pr. Chem.*, 1889, **40**, 4), sulphuric acid (70%; 150 g.), glycerol (35 g.), and sodium *m*-nitrobenzenesulphonate (40 g.) were refluxed with stirring for 5 hours; the temperature fell from 148° to 137°. The solution was diluted with water (200 c.c.), made alkaline with ammonia, and acidified with acetic acid. On concentration, 5-methylquinoline-8-carboxylic acid was obtained in colourless minute needles, m. p. 174° (Jakubowski, *Ber.*, 1910, **43**, 3026, gives m. p. 173—174°) (Found: C, 69·8; H, 4·8; N, 7·8. Calc. for $C_{11}H_9O_2N$: C, 70·0; H, 4·8; N, 7·5%). The silver salt was heated in a vacuum to give 5-methylquinoline, yellow oil, b. p. 262°/755 mm. (0·3 g.; 10%) (Jakubowski, *loc. cit.*, gives b. p. 253—255°/735 mm., and Gabriel and Thieme, *Ber.*, 1919, **52**, 1088, give b. p. 263—264°/753 mm.). It formed a styphnate, which crystallised from alcohol in greenish-yellow needles, m. p. 216° (Manske, Marion, and Leger, *Canadian J. Res.*, 1942, **20** *B*, 133, give m. p. 218°); and a picrate, yellow microscopic needles, m. p. 221° (Manske, Marion, and Leger, *loc. cit.*, give m. p. 223°).

5-Methoxyquinoline.—3-Nitro-*p*-anisidine (50 g.) was stirred with water (300 c.c.) and concentrated hydrochloric acid (90 c.c.) for 2 hours and the suspension diazotised by adding sodium nitrite (30 g.) in water (150 c.c.) during 30 minutes with external cooling. A little undiazotised amine was filtered off and the orange diazo-solution added gradually to a solution of cuprous cyanide (from 150 g. copper sulphate and 160 g. potassium cyanide in 1 l. of water) at 70—80°; after vigorous effervescence, an orange solid separated and was filtered off when cold. *3-Nitro-4-cyanoanisole* crystallised from alcohol in dark red needles, m. p. 138° (42 g.; 79·3%) (Found: C, 53·2; H, 3·95; N, 15·6. $C_8H_6O_3N_2$ requires C, 53·9; H, 3·35; N, 15·7%). This (50 g.) was reduced on the steam-bath with hydrochloric acid (15%; 600 c.c.) and granulated tin (150 g.). The pale yellow solution was filtered and made alkaline with sodium hydroxide, and the product was extracted with chloroform. *4-Cyano-m-anisidine* crystallised from aqueous alcohol in pale yellow prismatic needles, m. p. 92° (26·5 g.; 64%) (Found: C, 64·5; H, 5·5; N, 18·5. $C_8H_8O_2N_2$ requires C, 64·9; H, 5·4; N, 18·9%). 4-Cyano-*m*-anisidine (20 g.), sulphuric acid (70%; 110 c.c.), glycerol (35 g.), and sodium *m*-nitrobenzenesulphonate (40 g.) were refluxed with stirring for 3 hours (b. p. 145—137·5°). The solution was made alkaline with ammonia, cooled, filtered, acidified with acetic acid, and concentrated (300 c.c.). *5-Methoxyquinoline-8-carboxylic acid* crystallised from alcohol in very fine, colourless needles, m. p. 210° (5·5 g.; 20%) (Found: C, 65·1; H, 4·5; N, 6·0. $C_{11}H_9O_3N$ requires C, 65·5; H, 4·45; N, 6·9%). This acid (5 g.) was decarboxylated by heating its silver salt in a vacuum and gave *5-methoxyquinoline*, colourless oil, b. p. 282°/758 mm. (0·5 g.; 14%); the *picrate*, almost insoluble in alcohol, had m. p. 230° (Found: C, 49·8; H, 3·4; N, 14·1. $C_{10}H_9ON,C_6H_3O_7N_3$ requires C, 49·5; H, 3·1; N, 14·4%); the *oxalate*, pale yellow prismatic needles from alcohol, m. p. 156° [Found: C, 57·2; H, 4·5; N, 5·2; OMe, 11·5. $C_{10}H_9ON,(CO_2H)_2$ requires C, 57·8; H, 4·4; N, 5·6; OMe, 12·45%].

Orientation of 7-Substituted Quinoline Derivatives.

7-Methylquinoline.—3-Nitro-*o*-toluidine (15 g.) (Gabriel and Thieme, *Ber.*, 1919, **52**, 1079) was reduced with concentrated hydrochloric acid (50 c.c.) and granulated tin (20 g.) (Lellmann, *Annalen*, 1885, **228**, 243). 2 : 3-Diaminotoluene was extracted with ether and distilled as a red oil, b. p. 256°/750 mm., m. p. 60° (7 g.; 60%). The base reacted with phenanthraquinone in aqueous sodium hydrogen sulphite in presence of sodium acetate to give *6-methyl-1 : 2 : 3 : 4-dibenzphenazine*, which crystallised from alcohol in pale yellow, very fine needles, m. p. 223° (Found: C, 84·0; H, 4·8; N, 9·6. $C_{21}H_{14}N_2$ requires

C, 85·7; H, 4·75; N, 9·5%). 2 : 3-Diaminotoluene (7 g.), sulphuric acid (65%; 80 g.), glycerol (15 g.), and sodium *m*-nitrobenzenesulphonate (15 g.) were refluxed with stirring for 2·25 hours (b. p. 139—135°). The solution was made alkaline with sodium hydroxide and distilled with steam, and the 8-*amino*-7-*methylquinoline* was filtered off and dried in a desiccator (2·2 g.; 22%). It formed pale yellow microscopic needles, m. p. 38—40°, b. p. 306°/753 mm., containing water of crystallisation (Found : C, 69·2; H, 6·7; N, 15·5. $C_{10}H_{10}N_2,H_2O$ requires C, 68·2; H, 6·8; N, 15·9%); the *acetyl* derivative separated from aqueous alcohol (charcoal) in colourless crystals, m. p. 155° (Found : C, 71·3; H, 6·1; N, 14·3. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0; N, 14·0%). 8-Amino-7-methylquinoline (1·5 g.) was dissolved in water (100 c.c.) and hydrochloric acid (5 c.c.) and the orange solution diazotised at 0°. The diazo-solution was poured into boiling alcohol (95%; 150 c.c.) containing zinc dust (1 g.). Nitrogen was steadily evolved. After filtration, the solution was made strongly acid, alcohol evaporated, and the residual solution made alkaline with ammonia and distilled with steam. 7-Methylquinoline was extracted from the distillate with ether and distilled at 257°/756 mm. (0·3 g.; 22%); the picrate formed yellow microscopic needles almost insoluble in alcohol, m. p. 242°; the styphnate, yellow microscopic needles almost insoluble in alcohol, m. p. 242° (cf. Manske, Marion, and Leger, *loc. cit.*).

Quinoline-7-carboxylic Acid.—7-Methylquinoline was oxidised to quinoline-7-carboxylic acid (Skraup and Brünner, *Monatsh.*, 1886, **7**, 139), colourless crystals, m. p. 251° (Skraup and Brünner give m. p. 247°) (Found : C, 68·6; H, 4·3; N, 7·6. Calc. for $C_{10}H_7O_2N$: C, 69·3; H, 4·1; N, 8·1%), which was reduced to 1 : 2 : 3 : 4-tetrahydroquinoline-7-carboxylic acid (Fischer and Endres, *Ber.*, 1902, **35**, 2612), straw-coloured leaflets, m. p. 190°.

7-*Nitro-*, *-Amino-*, *and -Cyano-quinolines.*—7-Nitroquinoline, colourless needles, m. p. 136°, was reduced to 7-aminoquinoline (Kochanska and Brobanski, *loc. cit.*), long pale yellow needles, m. p. 94° (Found : C, 74·7; H, 5·6; N, 19·1. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·5; N, 19·5%); the acetyl derivative had m. p. 168·5° (Hamer, *loc. cit.*, gives m. p. 167·5°). 7-Aminoquinoline (6 g.) was converted into 7-*cyanoquinoline* (cf. Freydl, *loc. cit.*), which crystallised from aqueous alcohol (charcoal) in pale brown microscopic needles, m. p. 104° (Found : C, 77·7; H, 3·5; N, 17·0. $C_{10}H_6N_2$ requires C, 77·9; H, 3·9; N, 17·8%); the *picrate* had m. p. 249° (darkens at 200°) (Found : C, 49·7; H, 2·3; N, 17·8. $C_{10}H_6N_2,C_6H_3O_7N_3$ requires C, 50·2; H, 2·35; N, 18·3%); a *nitrate*, which crystallised from water in minute colourless needles, had m. p. 200° (Found : N, 18·7. $C_{10}H_6N_2,HNO_3$ requires N, 19·2%). 7-Cyanoquinoline was hydrolysed by refluxing with 60% sulphuric acid and gave quinoline-7-carboxylic acid, m. p. 251°, not depressed on admixture with the above quinoline-7-carboxylic acid obtained by oxidising 7-methylquinoline.

7-*Chloroquinoline.*—7-Aminoquinoline (6 g.) was dissolved in concentrated hydrochloric acid (25 c.c.) and water (25 c.c.) and the solution diazotised at 0° by adding sodium nitrite (5 g.) in water. The diazo-solution was poured into a cooled solution of cuprous chloride (4 g.) in hydrochloric acid (30%; 30 c.c.), and, after 5 minutes, the mixture was heated on the steam-bath for 30 minutes. The resulting mixture was made alkaline with sodium hydroxide and distilled with steam, and the 7-chloroquinoline was extracted from the distillate with ether. It crystallised from ether in colourless needles, m. p. 30°, b. p. 267—268° (3·8 g.; 59%) (Found : C, 65·6; H, 3·2; N, 8·05. Calc. for C_9H_6NCl : C, 66·1; H, 3·6; N, 8·6%); the dichromate formed yellow needles from hot water, m. p. 178° (decomp.); the *nitrate*, colourless, prismatic needles from water, m. p. 199° (Found : N, 11·9. C_9H_6NCl,HNO_3 requires N, 12·4%); the *oxalate*, colourless microscopic leaflets from alcohol, m. p. 155° [Found : C, 57·6; H, 3·3; N, 6·7. $(C_9H_6NCl)_2,(CO_2H)_2$ requires C, 57·7; H, 3·35; N, 6·7%].

7-*Bromoquinoline.*—7-Aminoquinoline (10 g.) was converted into 7-bromoquinoline, colourless needles, m. p. 35°, b. p. 288°/753 mm. (6·4 g.; 45%), in a similar manner to that already described for 5-bromoquinoline; the dichromate formed pale yellow needles from water, m. p. 202° (Claus and Tornier, *Ber.*, 1887, **20**, 2872, give m. p. 190°); the nitrate, colourless microscopic needles from water, m. p. 205—206° (decomp.) (Claus and Vis, *J. pr. Chem.*, 1888, **38**, 387, give m. p. 199°); the *oxalate*, colourless prisms from alcohol, m. p. 168° [Found : C, 47·1; H, 3·0; N, 4·7. $(C_9H_6NBr)_2,(CO_2H)_2$ requires C, 47·4; H, 2·75; N, 5·5%]; the *picrate*, almost insoluble in alcohol, yellow crystals, m. p. 238° (Found : N, 12·0. $C_9H_6NBr,C_6H_3O_7N_3$ requires N, 12·8%).

7-*Hydroxyquinoline.*—7-Aminoquinoline (5 g.) was converted into 7-hydroxyquinoline (Kochanska and Brobanski, *loc. cit.*), m. p. 238° (1 g.; 20%); the picrate formed yellow microscopic needles from alcohol, m. p. 245° (cf. Skraup, *Monatsh.*, 1882, **3**, 559); the *oxalate*, buff-coloured prisms from alcohol, m. p. 164° [Found : C, 64·3; H, 4·0; N, 7·0. $(C_9H_7ON)_2,(CO_2H)_2$ requires C, 64·6; H, 4·2; N, 7·5%]; the *nitrate*, pale brown needles from water, m. p. 151° (decomp.) (Found : N, 12·8. C_9H_7ON,HNO_3 requires N, 13·4%).

7-*Dimethylaminoquinoline.*—7-Bromoquinoline (4 g.) was heated with aqueous dimethylamin (33%; 20 c.c.) in a sealed tube at 250° for 8 hours. The resulting mixture was extracted with ether. The oil, b. p. 295—325°, contained unchanged 7-bromoquinoline. Purification was effected by fractional crystallisation of the perchlorate from alcohol. The perchlorate was made alkaline with sodium hydroxide and the mixture extracted with ether. 7-*Dimethylaminoquinoline* formed a yellow oil, b. p. 326°/751 mm. (Found : C, 75·9; H, 7·5; N, 16·6. $C_{11}H_{12}N_2$ requires C, 76·8; H, 7·0; N, 16·3%); the *perchlorate* formed minute orange needles from alcohol, m. p. 240° (Found : C, 48·8; H, 4·8; N, 10·4; Cl, 13·0. $C_{11}H_{12}N_2,HClO_4$ requires C, 48·4; H, 4·8; N, 10·3; Cl, 13·0%); the *oxalate*, minute orange needles from alcohol, m. p. 195° [Found : C, 59·7; H, 5·5; N, 9·9. $C_{11}H_{12}N_2,(CO_2H)_2$ requires C, 59·5; H, 5·35; N, 10·7%]; the *picrate*, almost insoluble in alcohol, orange-yellow crystals, m. p. 242° (Found : C, 51·1; H, 4·0. $C_{11}H_{12}N_2,C_6H_3O_7N_3$ requires C, 50·9; H, 3·8%). 7-Dimethylaminoquinoline was also obtained by heating 7-chloroquinoline with aqueous dimethylamine at 290° for 7 hours.

7-*Methoxyquinoline.*—7-Bromoquinoline (5 g.) was heated with a solution of sodium (2 g) in methyl alcohol (25 c.c.) at 250° for 7 hours. The resulting solution was acidified, alcohol evaporated, and the residue basified with sodium hydroxide and distilled with steam. The oil, extracted from the distillate with ether, contained no halogen and formed a *dichromate*, which crystallised from hot water in long, pale yellow needles, m. p. 210° [Found : C, 44·5; H, 3·85; N, 5·7; Cr_2O_3, 27·1. $(C_{10}H_9ON)_2,H_2Cr_2O_7$ requires C, 44·8; H, 3·7; N, 5·2; Cr_2O_3, 28·3%].

7-Chloro-8-methylquinoline.—6-Chloroacet-*o*-toluidide (20 g.), sulphuric acid (70%; 100 c.c.), glycerol (30 g.), and sodium *m*-nitrobenzenesulphonate (50 g.) were refluxed with stirring for 1·25 hours (b. p. 150—142°). The solution was diluted, diazotised, boiled to decompose any diazo-compounds, then made alkaline with sodium hydroxide and distilled with steam, and the distillate extracted with ether. *7-Chloro-8-methylquinoline* crystallised from aqueous alcohol in microscopic colourless needles, m. p. 45—48°, b. p. 278°/759 mm. (15 g.; 74%) (Found: C, 67·2; H, 4·25; N, 7·2. $C_{10}H_8NCl$ requires C, 67·6; H, 4·5; N, 7·9%); the *nitrate* formed colourless needles from water, m. p. 149° (Found: C, 49·9; H, 3·7. $C_{10}H_8NCl,HNO_3$ requires C, 49·9; H, 3·7%); the *oxalate*, colourless prisms from alcohol, m. p. 146° [Found: C, 58·6; H, 3·6; N, 5·7. $(C_{10}H_8NCl)_2(CO_2H)_2$ requires C, 59·3; H, 4·0; N, 6·3%]; the *perchlorate*, long colourless needles from alcohol, m. p. 171° (Found: C, 43·3; H, 3·9. $C_{10}H_8NCl,HClO_4$ requires C, 43·2; H, 3·2%); the *dichromate*, yellow prismatic needles from hot water, m. p. 148° [Found: C, 41·6; H, 3·2. $(C_{10}H_8NCl)_2,H_2Cr_2O_7$ requires C, 41·9; H, 3·1%].

Skraup Reaction with m-*Nitroaniline.*—A mixture of *m*-nitroaniline (30 g.), arsenic acid (80%; 125 g.), sulphuric acid (of concentration and amount as indicated in the table), and glycerol (in amount as indicated in the table) was refluxed with stirring until no unaltered *m*-nitroaniline could be detected. Boiling began at temperatures between 130° and 180° (depending on acid concentration), and the b. p. fell during the course of the reaction. The reaction mixture was diluted to 2 l. and filtered, then made alkaline with sodium hydroxide solution with the addition of ice to prevent the low-melting product from forming a tar. The greenish precipitate of nitroquinolines was filtered off and freed from inorganic matter by boiling with chloroform (300 c.c.; charcoal). After filtration, the chloroform layer was separated and the chloroform evaporated. The mixture of 5- and 7-nitroquinolines was dissolved in boiling water (300 c.c.) and concentrated nitric acid (25 c.c.) and cooled to 20°, and the precipitate of pure 5-nitroquinoline nitrate was filtered off. The filtrate was made alkaline with sodium hydroxide, and the precipitate collected, dried in a desiccator, refluxed with ligroin (b. p. 40—60°; 200 c.c.), and filtered through a hot funnel to separate the insoluble 7- from the 5-nitroquinoline. 5-Nitroquinoline crystallised in colourless plates, m. p. 71°, and formed a nitrate, pale yellow minute prisms, m. p. 195°, both of which were identical with the synthetic products already described. It formed an *oxalate* which crystallised from alcohol in colourless needles, m. p. 175° [Found: C, 54·8; H, 3·35. $(C_9H_6O_2N_2)_2,(CO_2H)_2$ requires C, 54·8; H, 3·2%]; a *perchlorate* which crystallised from aqueous alcohol in colourless needles, m. p. 167° [Found: Cl, 7·7. $(C_9H_6O_2N_2)_2,HClO_4$ requires Cl, 7·9%]; a *picrate*, insoluble in alcohol, m. p. 214° (Found: C, 45·1; H, 2·3. $C_9H_6O_2N_2,C_6H_3O_7N_3$ requires C, 44·7; H, 2·2%); a *dichromate*, yellow prisms, m. p. 129° [Found: C, 38·8; H, 3·0; Cr, 19·8. $(C_9H_6O_2N_2)_2,H_2Cr_2O_7$ requires C, 38·2; H, 2·5; Cr, 18·4%]; and a hydrochloride, straw-coloured needles, m. p. 224°. 7-Nitroquinoline crystallised in colourless needles, m. p. 136°, and formed an *oxalate*, colourless needles, m. p. 200° [Found: C, 54·9; H, 3·25. $(C_9H_6O_2N_2)_2,(CO_2H)_2$ requires C, 54·8; H, 3·2%]; a *picrate*, insoluble in alcohol, m. p. 217° (Found: C, 45·6; H, 2·35. $C_9H_6O_2N_2,C_6H_3O_7N_3$ requires C, 44·7; H, 2·2%); and a hydrochloride, straw-coloured needles, m. p. 234°.

Yield (%) of 5- and 7-nitroquinoline, and times of reaction.

Weight of glycerol (g.).	Concentration and quantity of sulphuric acid.					
	65%; 350 g.	70%; 350 g.	75%; 300 g.	80%; 300 g.	85%; 250 g.	90%; 250 g.
30	—	65 (5 hr.)	61 (1·5 hr.)	58 (0·5 hr.)	52 (0·25 hr.)	—
40	—	—	65 (1·25 hr.)	63·5 (0·5 hr.)	55 (0·25 hr.)	45 (5 min.)
50	—	77·3 (2·75 hr.)	64 (1 hr.)	—	53 (0·25 hr.)	—
60	75 (6·75 hr.)	74 (2·25 hr.)	—	60 (0·5 hr.)	—	—
70	74 (4·75 hr.)	—	57 (1 hr.)	—	—	—
80	—	62·7 (2·25 hr.)	—	—	—	—
90	62 (5·75 hr.)	—	—	—	—	—

The ratio of 5- to 7-nitroquinoline was determined from the weights of the pure compounds isolated and was 3·5 : 1, being independent of the concentration of sulphuric acid used.

Skraup Reaction with m-*Toluidine.*—A mixture of *m*-toluidine (30 g.), glycerol (50 g.), sodium *m*-nitrobenzenesulphonate (80 g.), and sulphuric acid (of concentration and amount as indicated in the table) was refluxed with stirring for various times (b. p. between 139° and 162°). The mixture was diluted with water (200 c.c.), cooled, treated with excess of sodium nitrite (25 g.), and the solution boiled to decompose any unchanged *m*-toluidine, then made alkaline with sodium hydroxide and distilled with steam. The sole product was 7-methylquinoline, which was extracted with ether and distilled, b. p. 257°/754 mm. It formed a picrate, yellow microscopic needles, m. p. 242°, and a styphnate, yellow microscopic needles, m. p. 242°, both of which were identical with the synthetic products already described.

Yield (%) of 7-methylquinoline.

Time (hrs.).	Concentration and quantity of sulphuric acid.			
	65%; 250 g.	70%; 250 g.	75%; 200 g.	80%; 200 g.
0·5	—	42	59	—
0·75	—	—	—	73
1	—	53	64	73
2	36	61	71	—
2·5	—	—	—	73
3	40	70	74	—
4	43	69	74	—
5	43	—	—	—

Skraup Reaction with m-*Aminobenzoic Acid.*—A mixture of *m*-aminobenzoic acid (30 g.), glycerol (50 g.), sodium *m*-nitrobenzenesulphonate (60 g.), and sulphuric acid (of concentration and amount as indicated in the table) was refluxed with stirring for various times. The mixture was diluted with water (250 c.c.), made weakly alkaline with ammonia (*d* 0·880), then stirred well with charcoal (10 g.). The coagulated tar was filtered off, and the filtrate (800 c.c.) boiled (charcoal; 5 g.) and filtered. The clear red-brown solution was cooled to 50° and acidified with glacial acetic acid (15 c.c.), and the precipitate filtered off. The filtrate was concentrated to 400 c.c. and cooled; a second precipitate so obtained was washed free from ammonium sulphate. The first precipitate was boiled with water (600 c.c.) and glacial acetic acid (10 c.c.), and the insoluble quinoline-5-carboxylic acid filtered off hot. The filtrate was concentrated to 100 c.c. and cooled, and a precipitate of quinoline-7-carboxylic acid was obtained. The second precipitate, which consisted of quinoline-7-carboxylic acid containing inorganic matter, was dissolved in water (75 c.c.) and ammonia, and on acidification with acetic acid gave a precipitate of pure quinoline-7-carboxylic acid. In no case was any unaltered *m*-aminobenzoic acid detected. Quinoline-5-carboxylic acid formed colourless crystals, m. p. 342°, and formed a tetrahydro-derivative, colourless needles, m. p. 147°, both identical with the synthetic products already described. Quinoline-7-carboxylic acid formed colourless crystals, m. p. 251°, and formed a tetrahydro-derivative, straw-coloured leaflets, m. p. 190°, both identical with the synthetic products already described.

Yield (%) *of quinoline-5- and -7-carboxylic acids.*

	Concentration and quantity of sulphuric acid.		
Time (hrs.).	65%; 250 g.	70%; 250 g.	75%; 200 g.
1	—	54	56
2	38	61	35
3	—	70	—
4	—	66	—
4·5	60	—	—
6	63	—	—

The ratio of quinoline-5- to -7-carboxylic acid was 5 : 1 and was independent of the concentration of sulphuric acid used.

Skraup Reaction with m-*Aminodimethylaniline.*—A mixture of *m*-acetamidodimethylaniline (39 g.), glycerol (50 g.), sodium *m*-nitrobenzenesulphonate (60 g.), and sulphuric acid (70%; 250 g.) was refluxed with stirring for 5 hours. The mixture was diluted with water (100 c.c.) and basified with ammonia (*d* 0·880) which precipitated a considerable amount of tar. The mixture was extracted with ether, the ether removed, and the residue distilled as a yellow oil, b. p. 290—326° (10 g.; 27%). It was dissolved in boiling alcohol (75 c.c.) and to the solution was added an aqueous solution of perchloric acid (20%; 30 c.c.). On cooling, pure 7-dimethylaminoquinoline perchlorate (11 g.), m. p. 240°, was precipitated. The filtrate was basified with sodium hydroxide and extracted with ether, and the ether removed. The residual brown oil was dissolved in boiling alcohol (20 c.c.) and a solution of picric acid (2·5 g.) in boiling alcohol (10 c.c.) was added. The orange-yellow precipitate, m. p. *ca.* 175°, was boiled with alcohol (250 c.c.) and the insoluble residue (1 g.), m. p. 220°, was filtered off. After crystallisation from alcohol, it had m. p. 242° and was identical with 7-dimethylaminoquinoline picrate. The alcoholic filtrate after removal of the above residue, m. p. 220°, was concentrated to 100 c.c. and cooled, and gave an orange-yellow crystalline precipitate (2·5 g.), m. p. 184°. This picrate was basified with sodium hydroxide and extracted with ether, the ether removed, and the residue of *5-dimethylaminoquinoline* distilled as a yellow oil, b. p. 292°/741 mm. (1 g.) (Found: C, 76·0; H, 7·4; N, 16·3. $C_{11}H_{12}N_2$ requires C, 76·8; H, 7·0; N, 16·3%). It formed a *picrate*, orange-yellow microscopic needles, m. p. 184° (Found: C, 50·6; H, 3·6; N, 17·8. $C_{11}H_{12}N_2,C_6H_3O_7N_3$ requires C, 50·9; H, 3·7; N, 17·5%); and a *styphnate*, orange-yellow minute prisms, m. p. 215° (Found: C, 48·6; H, 3·6; N, 16·2. $C_{11}H_{12}N_2,C_6H_3O_8N_3$ requires C, 48·9; H, 3·6; N, 16·8%). When 65% sulphuric acid was used, the reaction was incomplete in 7 hours, and with 75% sulphuric acid the yield was the same as with 70% acid, but the reaction was complete in 5 hours. The ratio of 7- to 5-dimethylaminoquinoline was about 7 : 1, but this is probably only an approximation owing to the difficulty in separating the isomers.

7-Dimethylaminoquinoline formed a *styphnate*, orange-yellow microscopic needles, m. p. 225° (Found: C, 48·8; H, 3·9. $C_{11}H_{12}N_2,C_6H_3O_8N_3$ requires C, 48·9; H, 3·6%); a *dichromate*, orange microscopic needles, m. p. 152° (decomp.) [Found: C, 46·6; H, 3·9; N, 10·35; Cr, 19·1. $(C_{11}H_{12}N_2)_2,H_2Cr_2O_7$ requires C, 47·0; H, 4·6; N, 9·95; Cr, 18·5%]; and a *methiodide*, prepared by adding methyl iodide without warming, orange minute prisms, m. p. 257° (Found: I, 41·8. $C_{12}H_{15}N_2I$ requires I, 40·4%).

Skraup Reaction with m-*Chloroaniline.*—*m*-Chloroaniline (30 g.), sulphuric acid (of concentration and amount as indicated in the table), glycerol (45 g.), and sodium *m*-nitrobenzenesulphonate (70 g.) were refluxed with stirring for the time indicated. Boiling began at temperatures between 130° and 170°, and the b. p. fell during the course of the reaction. The cooled reaction mixture was treated with excess of sodium nitrite (up to 30 g.), and the solution boiled to decompose any unaltered *m*-chloroaniline, then made alkaline with sodium hydroxide and distilled with steam. The resulting mixture of 5- and 7-chloroquinolines was extracted with ether and distilled (yields given are weights of the distillate). This mixture was separated into the isomers by fractional crystallisation of the mixture of dichromates obtained by adding the theoretical amount of potassium (or sodium) dichromate to a very dilute solution of the bases in sulphuric acid (just acid to Congo-red). 7-Chloroquinoline, obtained from the dichromate fraction, m. p. 178°, after basification and distillation with steam, crystallised in colourless needles, m. p. 30°, b. p. 267—268°, and formed a nitrate, colourless, prismatic needles, m. p. 199°, and an oxalate, colourless microscopical leaflets, m. p. 155° (all identical with the synthetic products already described). It also formed a *perchlorate*, small colourless needles from ethyl acetate, m. p. 126° (Found: C, 40·1; H, 2·5. $C_9H_6NCl,HClO_4$ requires C, 40·9; H, 2·65%); and a *picrate*, almost insoluble in alcohol, m. p. 225° (Found: N, 14·9. $C_9H_6NCl,C_6H_3O_7N_3$ requires N, 14·25%).

5-Chloroquinoline, colourless needles, m. p. 43°, b. p. 256—257°, was obtained from the dichromate fraction, m. p. 110—120°, and filtrates after purification through the sparingly alcohol-soluble oxalate, colourless needles, m. p. 145°; it formed a nitrate, colourless prismatic needles, m. p. 159—161°, a perchlorate, colourless microscopic needles, m. p. 198° (all being identical with the synthetic products already described), and a lemon-yellow *picrate*, almost insoluble in alcohol, m. p. 220° (Found : N, 13·6. $C_9H_6NCl,C_6H_3O_7N_3$ requires N, 14·25%).

The ratio of 7- to 5-chloroquinoline was determined from the weights of the pure compounds isolated, losses during separation amounting to about 10%.

Yield (%) *of* 5- *and* 7-*chloroquinolines.*

	Concentration and quantity of sulphuric acid.				
Time (hrs.).	60%; 170 c.c.	65%; 155 c.c.	70%; 140 c.c.	75%; 125 c.c.	80%; 115 c.c.
0·5	—	—	40	83	70
1·25	—	36	70	82	—
2	30	52	83	80	62
2·75	—	65	88	78	—
3·5	38	66	91	—	—
4·25	40	—	—	—	—
5	43	—	—	—	—
Ratio of 7- to 5-chloroquinoline	1·4 : 1	1·6 : 1	2·7 : 1	3·4 : 1	3·9 : 1

The use of 85% sulphuric acid (105 c.c.), glycerol being added gradually in order to control the violence of the reaction, gave 7- and 5-chloroquinoline in 40% yield in the ratio of 4·4 : 1.

Skraup Reaction with m-*Bromoaniline.*—*m*-Bromoaniline (30 g.), sulphuric acid (of concentration and amount as indicated in the table), glycerol (45 g.), and sodium *m*-nitrobenzenesulphonate (70 g.) were refluxed with stirring for the time indicated (b. p. between 130° and 160°). The 5- and 7-bromoquinolines were isolated as described above for the chloro-analogues by fractional crystallisation of the dichromates. 5-Bromoquinoline, obtained by basification and steam distillation of the dichromate fraction, m. p. 133°, crystallised in colourless needles, m. p. 46—48°, b. p. 280°/759 mm.; and 7-bromoquinoline, obtained from the dichromate fraction, m. p. 202°, crystallised in colourless needles, m. p. 35°, b. p. 289°/759 mm.; they were identical with the synthetic products already described.

Yield (%) *of* 5- *and* 7-*bromoquinolines.*

	Concentration and quantity of sulphuric acid.			
Time (hrs.).	60%; 170 c.c.	65%; 155 c.c.	70%; 140 c.c.	75%; 125 c.c.
0·5	—	—	66·2	71·7
1·25	—	49·6	—	60·6
2	33·1	—	66·2	46·9
2·75	—	66·2	—	—
3·5	49·6	71·7	60·6	—
4·25	51·9	—	—	—
Ratio of 7- to 5-bromoquinoline	1·014 : 1	1·018 : 1	1·017 : 1	0·991 : 1

Skraup Reaction with m-*Aminophenol.*—*m*-Aminophenol (10 g.), sulphuric acid (65%; 100 g.), glycerol (20 g.), and sodium *m*-nitrobenzenesulphonate (20 g.) were refluxed with stirring for 4·5 hours (b. p. 139—134°). Sodium hydroxide was then added until the mixture was just acid to Congo-red, the mixture filtered, and excess of sodium carbonate added to the filtrate to precipitate 7-hydroxyquinoline (5·9 g.; 46%). This crystallised from chlorobenzene in pale yellow needles, m. p. 238°; the picrate formed yellow microscopic needles, m. p. 245°, and the nitrate, pale brown needles, m. p. 151° (decomp.) (all being identical with the synthetic products already described). The use of 70% sulphuric acid (95 g.) in a parallel experiment (b. p. 148—138°) for 3·5 hours gave solely 7-hydroxyquinoline (3·8 g.; 30%). The use of 60% sulphuric acid (80 c.c.), however, in a similar experiment (b. p. 135—131°) for 7·5 hours gave a product (7·6 g.; 60%), m. p. 210—234°, which formed an oxalate, m. p. 154°, and a picrate, m. p. 140—240°, the latter being separated into a fraction, m. p. 245°, identical with 7-hydroxyquinoline picrate, and a residue, m. p. 140—150°, indicating the possible presence of a little 5-hydroxyquinoline picrate.

Skraup Reaction with m-*Anisidine.*—A mixture of *m*-anisidine (20 g.), sulphuric acid (70%; 110 c.c.), glycerol (35 g.), and sodium *m*-nitrobenzenesulphonate (50 g.) was refluxed with stirring for 3 hours. The mixture was diluted with water and cooled, and excess of sodium nitrite added. The solution was boiled to decompose unaltered *m*-anisidine, then made alkaline with sodium hydroxide and distilled with steam. The product, consisting solely of 7-methoxyquinoline, was extracted with ether and distilled as a yellow oil, b. p. 287°/758 mm. (7 g.; 27%) (Found : C, 75·3; H, 5·4; N, 9·2; OMe, 19·0. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·65; N, 8·8; OMe, 19·5%); the dichromate, pale yellow needles, m. p. 210°, was identical with the synthetic product already described. It also formed a picrate, m. p. 229° (Robinson and Lempert, *J.*, 1934, 1419, give m. p. 216°) (Found : C, 49·4; H, 3·2; N, 15·2. Calc. for $C_{10}H_9ON,C_6H_3O_7N_3$: C, 49·5; H, 3·1; N, 14·4%); an *oxalate*, colourless needles, m. p. 126° [Found : C, 57·3; H, 4·1; N, 5·65. $C_{10}H_9ON,(CO_2H)_2$ requires C, 57·8; H, 4·4; N, 5·6%]; and a methiodide, yellow prismatic needles, m. p. 210° (Robinson and Lempert, *loc. cit.*, give m. p. 204°). The use of 65% and 75% sulphuric acid did not alter the yield.

Skraup Reaction with Metanilic Acid.—Metanilic acid (30 g.), sulphuric acid (70%; 130 c.c.), glycerol (40 g.), and nitrobenzene (35 g.) were refluxed with stirring for 3 hours (b. p. 148—137°). Water (200 c.c.) was then added, nitrobenzene removed by steam distillation, and the solution basified with excess of an aqueous suspension of calcium hydroxide. After filtration, the filtrate was boiled (charcoal), neutralised with dilute sulphuric acid, filtered, boiled (charcoal), filtered, and concentrated. Fractions were filtered off at intervals and a final fraction obtained by adding alcohol to the viscous residue (total, 18·7 g.; 51·5%). The first fraction crystallised from water in colourless, well-formed plates, decomposing above 350°. After drying for several hours at 100°, the crystals still contained water and were hygroscopic (Found: C, 49·6; H, 3·85; N, 7·3; S, 15·4. Calc. for $C_9H_7O_3NS$: C, 51·7; H, 3·35; N, 6·7; S, 15·3%).

The sulphonic acid (20 g.) was dissolved in water (200 c.c.) and the solution evaporated until 9·5 g. had crystallised. The remaining sulphonic acid (10·5 g.) was converted into a mixture of cyanoquinolines (cf. Lellmann and Lange, *Ber.*, 1887, **20**, 1446), but the conversion was far from complete (1·5 g.; 20%). The mixture of cyanoquinolines was hydrolysed with 50% sulphuric acid to a mixture of quinoline carboxylic acids (1·1 g.) which was separated by the method already described under the Skraup reaction with *m*-aminobenzoic acid. Quinoline-5-carboxylic acid (0·2 g.), colourless crystals, m. p. 342°, and quinoline-7-carboxylic acid (0·6 g.), colourless crystals, m. p. 251°, were obtained, identical with the synthetic products already described. When the sulphonic acid was used without separating the more insoluble fraction, only quinoline-5-carboxylic acid could be isolated after hydrolysis of the cyanoquinoline, indicating that quinoline-5-sulphonic acid preponderated in the mixture.

When 60% sulphuric acid was used, the reaction was incomplete after 8 hours, but with 65% sulphuric acid the yield was 75% after 3 hours, and with 70% sulphuric acid the yield was 77% after 0·5 hour, this product containing no unaltered metanilic acid.

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89. *The Structures of Hantzsch's Isomeric Diazocyanides.*

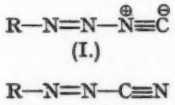
By D. ANDERSON, R. J. W. LE FÈVRE, and J. SAVAGE.

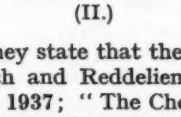
The chemical evidence upon which Hodgson and Marsden recently proposed that Hantzsch's *syn*- and *anti*-diazocyanides are related as *iso*- and *n*-cyanides respectively is shown as equivocal and not incompatible with the view that these substances are geometrically isomeric cyanides. Recorded dipole moments and refractivity data are also against Hodgson's hypothesis.

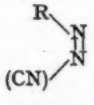
Infra-red spectra are now described of *syn*- and *anti*-*p*-chloro-, -*p*-bromo-, and -*p*-nitrobenzen diazocyanides, together with those of the two known 4:4'-diphenylbisdiazocyanides. Frequencies associated with cyanide, rather than *iso*cyanide, groups occur as common features throughout. Thus further support is provided for Hantzsch's formulations.

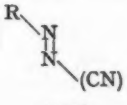
Between 800 and 900 cm.$^{-1}$, a regular peculiarity of the spectra of each isomeric pair of benzene derivatives is noted; this, when applied to the diphenylbisdiazocyanides, indicates that the allotment of configurations made earlier (by dipole-moment evidence) is probably correct.

THE proposition that Hantzsch's *syn*- and *anti*-diazocyanides would be more appropriately represented as structural (I and II), than as geometrical (III and IV), isomers was recently discussed by Hodgson and Marsden (*J.*, 1944, 395). Their argument falls into three sections.


(I.)


(II.)


(III.)


(IV.)

First, they state that the recorded reactions of these substances (" Die Diazo Verbindungen ", Hantzsch and Reddelien, 1921; " Organic Chemistry of Nitrogen ", Sidgwick and Taylor, Oxford, 1937; " The Chemistry of the Diazo-Compounds and Their Technical Applications ", Saunders, London, 1936) are in general " entirely in favour of Orton's view (*J.*, 1903, **83**, 796) that the *syn*- and *anti*-diazocyanides are the diazo*iso*nitriles and diazonitriles respectively ".

Secondly, they state that Le Fèvre and Vine's dipole-moment data (*J.*, 1938, 431) " are, in a broad qualitative way, not really antagonistic to the structural formulation. . . . Resonance will probably account for numerical details.". Thirdly, they describe new applications of the Grignard reagent to this problem, and then state that " Hantzsch's stereo-formulation of the aryl *syn*-diazocyanides will not explain (*a*) the formation of complexes with methylmagnesium iodide or phenylmagnesium bromide, in dry ethereal solution, leading eventually on hydrolysis to acetaldehyde and benzaldehyde, respectively, and the non-formation of an aldehyde with corresponding reactions of the *anti*-isomerides . . ."

Comments on Hodgson and Marsden's Three Arguments.—(1) *General chemistry of diazocyanides.* We are not convinced that Hodgson and Marsden (*loc. cit.*) have drawn the only possible conclusion from their review of the older literature on the diazocyanides. Such properties as relative speeds of coupling, ionisation, etc., do not, we submit, necessitate the possession by *syn*-compounds of the readily broken N–N bond, and by *anti*- of the more stable C–N link.

Similar, although less marked, contrasts are often shown by geometrical isomers. The oximes present the most relevant analogies, in that they frequently show notable differences in stability, particularly as derivatives; *e.g.*, the reactivities of the acetylated aldoximes under hydrolysis (Hantzsch, *Ber.*, 1891, **24**, 13; Wentworth and Brady, *J.*, 1920, **117**, 1045). With the parent substances, when these differences are great, only one form is known (particularly with aryl oximes, Brady and Dunn, *J.*, 1914, **105**, 821, 2409; 1915, **107**, 1858; 1916, **109**, 667; Wentworth and Brady, *loc. cit.*; Brady, Cosson, and Roper, *J.*, 1925, **127**, 2427; Brady and Bennett, *J.*, 1927, 894); when they are less, it is sometimes possible to interchange the forms by the action of light (Ciamician and Silber, *Ber.*, 1902, **35**, 4128; 1903, **36**, 4268; Brady and Klein, *J.*, 1927, 874). The isomeric oximes have different dissociation constants (Brady and Goldstein, *J.*, 1926, 1918).

Above all, the existence of azobenzene in *cis*- and *trans*-forms, both fully examined chemically and physically (Hartley, *J.*, 1938, 633; Le Fèvre and Hartley, *J.*, 1939, 531; Robertson, *J.*, 1939, 232; de Lange, Robertson, and Woodward, *Proc. Roy. Soc.*, 1939, *A*, **171**, 398), clearly shows that geometrical isomerism about the –N=N– system *is* possible. Moreover the properties of the two azobenzenes, although dissimilar in many features, are quite in harmony with recorded knowledge of geometrical isomerism, and—where comparison is reasonable—have close analogies in the diazocyanides (Hartley; Le Fèvre and Vine, *locc. cit.*).

We conclude, therefore, that geometrical isomerism need not be excluded on general grounds.

(2) *Dipole moments of diazocyanides.* Le Fèvre and Vine (*loc. cit.*) did not allude to the possibility of a cyanide–*iso*cyanide relationship when discussing their results. Fortunately, the required dipole-moment data exist to enable this point to be examined. The figures shown in Table I were recorded by Poltz, Steil, and Strasser (*Z. physikal. Chem.*, 1932, *B*, **17**, 155—160), Wolfe and Strasser (*ibid.*, 1933, *B*, **21**, 389), and Hammick, New, Sidgwick, and Sutton (*J.*, 1930, 1876). It will be noted that the moment of phenyl cyanide is only slightly greater than that of

TABLE I.

Benzene derivative.	Moment, D.	Phenyl cyanide derivative.	Moment, D.	Phenyl *iso*cyanide derivative.	Moment, D.
Me	0·4	*p*-Me	4·37	*p*-Me	3·96 3·98 *
Cl	1·55	*p*-Cl	2·51	*p*-Cl	2·08 2·07 *
Br	1·52	*p*-Br	2·64		
NO_2	3·90	*p*-NO_2	<0·7 0·66 *		
CN	3·94				
NC	3·53				

* Figures from Hammick, New, Sidgwick, and Sutton (*loc. cit.*).

phenyl *iso*cyanide. Electron-diffraction and spectroscopic studies (Brockway, *J. Amer. Chem. Soc.*, 1936, **58**, 2516; Gordy and Pauling, *ibid.*, 1942, **64**, 2952; Badger and Bauer, *ibid.*, 1937, **59**, 303) have indicated that CH_3·NC is a linear molecule to within 20°. All this, together with the fact (New and Sutton, *J.*, 1932, 1415) that 1 : 4-di*iso*cyanobenzene has a vanishingly small moment, justifies a view that the vectors arising from the cyanide and *iso*cyanide groups resemble one another in magnitude and direction and lie closely along the axis of the single links, Ar–CN and Ar–NC, in the two sets of compounds.

Now such a similarity of μ_{CN} and μ_{NC} means that the latter could be inserted into Le Fèvre and Vine's reasoning in place of the former. It is, therefore, clear that vectorial analysis of experimentally obtained values will not alone decide whether, if these compounds *are cis*- and *trans*-forms, the carbon and nitrogen atoms occur as the *iso*cyanide group in the former series and/or as the cyanide group in the latter.

However, although not explicity stated, Hodgson and Marsden's reference to Orton's paper indicates their acceptance of an extended *trans*- or linear configuration throughout, with the essential difference between the isomers being the possession of normal and *iso*-groups in the stable or labile forms respectively. Such a proposal can be easily tested, since in each case both members of the isomeric pairs (*a*) might be expected to have *roughly* the same moment, or (*b*), if their moments are not equal, show an approximate constancy of inequality throughout all

the known examples. Reference to Table II makes it clear that neither of these forecasts is fulfilled.

TABLE II.

Diazobenzene cyanide derivative.	Dipole moments found : labile form.	stable form.	Differences, $\mu_{labile} - \mu_{stable}$.
4-Chloro-	2·93	3·73	−0·80
4-Bromo-	2·91	3·78	−0·87
4-Nitro-	2·04	1·47	−0·57
2 : 4 : 6-Tribromo-	2·5	4·0	+1·5

We conclude, therefore, that dipole moment data can eliminate a structural hypothesis in which both forms are *trans*.

(3) *The Grignard reactions.* The isolation of aldehydes is represented by Hodgson and Marsden as follows :

$$C_6H_4R\cdot N{:}N\cdot \overset{+}{N}{:}\overset{-}{C} + MgIMe \xrightarrow{Et_2O} C_6H_4R\cdot N{:}N\cdot N{:}CMe\cdot MgI \xrightarrow{Hydrolysis}$$

$$C_6H_4R\cdot N{:}N\cdot N{:}CHMe \xrightarrow[hydrolysis]{Further} CH_3\cdot CHO$$

and the analogy with the corresponding reactions of *iso*cyanides is advanced to support their allotment of this structure to (CN) groups in the *syn*-series.

Alternative possibilities are not discussed—notably the possible relevance of the observation by Stephenson and Waters (*J.*, 1939, 1796) that ethereal solutions of the *syn*-diazocyanides undergo purely catalytic decompositions by copper powder to aromatic *cyanides*, the corresponding hydrogen-substituted products, *and acetaldehyde*. The last-named could, therefore, have arisen in Hodgson's experiments from the solvent and be without significance to his main thesis.

These crucial Grignard reactions are recorded rather briefly, yields of acetaldehyde from methylmagnesium iodide greater than 20% on the weight of *syn*-diazocyanide taken are not claimed, and the identification of the aldehydes, from either methylmagnesium iodide or phenylmagnesium bromide, as their nitro- or dinitro-phenylhydrazones, is asserted without descriptive detail. For the important case of acetaldehyde this procedure is especially unsound in view of the uncertainty of melting point and suspected polymorphism of its 2 : 4-dinitrophenylhydrazone (Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955; Cameron and Storrie, *J.*, 1934, 1330; Ingold, Pritchard, and Smith, *ibid.*, p. 79; Bryant, *J. Amer. Chem. Soc.*, 1933, **55**, 3201; Campbell, *Analyst*, 1936, **61**, 391; Allen and Richmond, *J. Org. Chem.*, 1937, **2**, 222; Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 758). Further, we have found that the dinitrophenylhydrazones of the simpler aldehydes and ketones do not greatly depress one another's m. p.s (cf. Brandstätter, *Mikrochem.*, 1944, **32**, 33) so that mixed m. p. determinations (if these were used) could not have been relied upon to establish identity. Extinction angles under the polarising microscope, however, can be usefully applied in the matter.

At the outset we repeated Hodgson and Marsden's directions many times and confirmed the formation of acetaldehyde in ethyl ether as a medium. The yield (as dinitrophenylhydrazone), slightly improved by omitting the 15 mins.' boiling (*loc. cit.*, p. 398, line 8 of Experimental), was always impure, and only showed the correct properties after several crystallisations. At least one of the accompanying derivatives, *viz.*, acetone 2 : 4-dinitrophenylhydrazone, has been separated from the total crude product.

We have also examined the interaction of methylmagnesium iodide with various of the *syn*-diazocyanides in anisole or *iso*amyl ether. Dinitrophenylhydrazones were obtained in small amounts. These we failed to resolve into pure components although, in cases where amyl ether was used, experimental evidence indicated the final presence of a derivative of *iso*valeraldehyde.

Nevertheless, both Hodgson's experiments and ours can easily be understood if, following Stephenson and Waters (*loc. cit.*), the *syn*-diazocyanides undergo fission, even momentarily, in solution to give two neutral free radicals :

$$R\cdot N_2\cdot CN \longrightarrow R\cdot N_2\cdot + \cdot CN$$

followed, *e.g.*, by

$$OEt_2 + \cdot CN \longrightarrow HCN + \cdot C_2H_4\cdot OEt$$

and eventually

$$HCN + MgIMe \longrightarrow \text{etc.} \longrightarrow CH_3\cdot CHO$$

It is true that Stephenson and Waters demonstrated this type of fission in the presence of copper; they emphasised, however, the fact that the metal was completely unaffected. With other diazo-compounds, *e.g.*, benzene*iso*diazoacetate (Waters, *J.*, 1937, 113), analogous decompositions, *in which acetaldehyde is also produced from ethyl ether*, took place spontaneously at ordinary temperatures *without* a catalyst being necessary. Many reactions other than the above can also occur (cf. Waters, *loc. cit.*; Grieve and Hey, *J.*, 1934, 1797; Hey and Waters, *Chem. Revs.*, 1937, **21**, 169) and may easily explain low yields of aldehydes and the formation of large amounts of nitrogenous tars in the present work.

The simultaneous production of acetone during these Grignard reactions could either be effected *via* a simple double decomposition :

$$R{\cdot}N_2{\cdot}CN + MgIMe \longrightarrow R{\cdot}N_2{\cdot}MgI + Me{\cdot}CN \xrightarrow[\text{etc.}]{MgIMe,} COMe_2$$

or—Grignard reagents themselves being a fruitful source of free radicals (Hey, *Ann. Reports*, 1940, **37**, 285; 1944, **41**, 181)—the intermediate methyl cyanide could be formed directly :

$$Me\cdot + \cdot CN \longrightarrow MeCN.$$

We conclude, therefore, that Hodgson and Marsden's Grignard reactions do not necessitate an *iso*cyanide structure for the *syn*-diazocyanides.

Recorded Physical Evidence bearing on the Problem.—Apart from the dipole-moment measurements already mentioned, refractometric data indicate a definite conclusion. Le Fèvre and Vine (*loc. cit.*, p. 433), observing that the *stable* member of each pair of diazocyanides had the *greater* molecular refraction, commented that this was the relationship common throughout geometrical isomerism, a fact which supported the idea that the *syn-* and *anti*-forms are *cis-* and *trans-*, respectively. The structural hypothesis (I and II) was not mentioned.

The actual refractions (Table III) can be considered *vis-à-vis* the values for known cyanides and *iso*cyanides, *e.g.*, Ph·CN, $[R_L]_D = 31{\cdot}62$ c.c.; Ph·NC, $[R_L]_D = 32{\cdot}32$ c.c. (these figures evidently are not much affected by conjugation between the substituent and the aromatic nucleus since similar differences occur with aliphatic derivatives, *e.g.*, Et·CN, $[R_L]_\alpha = 15{\cdot}71$ c.c.; Et·NC, $[R_L]_\alpha = 16{\cdot}45$ c.c.). Von Auwers (*Ber.*, 1927, **60**, 2137) summarises the matter by quoting $[R_L]_D$ group refractions as 5·415 c.c. for the cyanide group; 6·136 for the *iso*cyanide group. Formulæ of type (I) and (II) would therefore require the refractions of the unstable varieties to be greater than their stable (*trans-*) isomers. Experiment demonstrates the reverse order.

TABLE III.

Diazobenzene cyanide derivative.		4-Cl.	4-Br.	4-NO_2.	2-Br.	2 : 4-Br_2.	2 : 4 : 6-Br_3.
$[R_L]_D$ value	Stable form	48·0	52·3	48·6	51·6	58·64 *	68
	Unstable form	46·1	49·9	44·7	47·2	56·59 *	64

(Data from Le Fèvre and Vine, *loc. cit.*, and Bruhl, *Ber.*, 1896, **29**, 2907—the latter are asterisked.)

Spectroscopic and conductometric (Hantzsch, *Ber.*, 1900, **33**, 2177) information is also available. Neither is very helpful. Hantzsch and Lifschitz (*Ber.*, 1912, **45**, 3011) and Le Fèvre and Vine (*loc. cit.*) have reported absorption spectra in the visible and the near ultra-violet region, but their findings do not add to the evidence for either view. This might be expected since, where the cyanide–*iso*cyanide question is concerned, Wolf and Strasser (*Z. physikal. Chem.*, 1933, *B*, **21**, 389) have found that the phenyl, *p*-tolyl, and *p*-chlorophenyl cyanides and *iso*cyanides show no remarkable spectrum differences in hexane or heptane between 2200 and 2850 A., while *apropos* geometrical isomerism, it is well known that the spectra of such isomerides need not be dissimilar.

It seemed to us that important results might be achieved by the use of longer wave-lengths; this followed, since Dadieu (*vide* Hibben, " The Raman Effect and its Chemical Application ") has found certain notable differences between the Raman spectra of isomeric nitriles and *iso*cyanides—differences which are appropriately detected in the related infra-red spectra (see below). The remainder of the present paper is chiefly concerned with observations arising from this point.

Infra-red Absorption Spectra of Isomeric Diazocyanides.—These have been measured over the range 4—14 μ by using the Hilger Infra-red Prism Spectrometer as a single-beam instrument with photographic recording. The rock-salt prism was of the 30° Littrow type, and the instrument incorporated a Hilger–Schwarz vacuum thermopile.

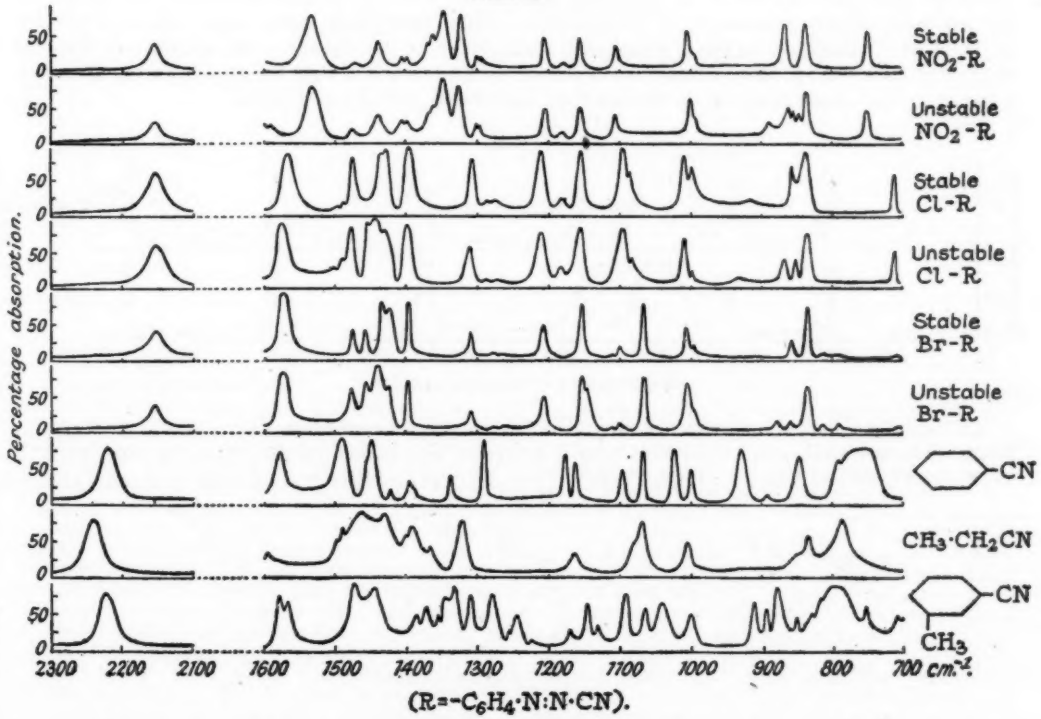
The spectrometer was calibrated in the region 6—14 μ by using the absorption bands of

ammonia, water, and carbon dioxide, as described by Oetjen, Chao-Lan Kao, and Randall (*Rev. Sci. Instr.*, 1942, **13**, 515); in that from 3—5 μ, by using liquid benzene, and applying the benzene absorption frequencies given by Bailey, Hall, Ingold, and Thompson (*J.*, 1931, 931).

The cyanides were examined in solution in carbon tetrachloride and carbon disulphide from 4 to 12 and 12 to 14 μ, respectively. Solutions were prepared by mixing an excess of the compound with the solvent in the dark, and filtering the solution into a rock-salt cell, having a thickness of about 0·1 mm. In addition to the diazo-cyanides, the absorption spectra of phenyl, *m*-tolyl, and ethyl cyanides were determined. The spectra are reproduced in Figs. 1 and 2.

It has been shown by Gordy and Williams (*J. Chem. Physics*, 1935, **3**, 664; 1936, **4**, 85), who studied various organic cyanides and corresponding *iso*cyanides, that the absorption frequency due to the CN valency vibration, occurring at about 2250 cm.$^{-1}$ (4·45 μ) for the cyanides, was shifted by about 100 cm.$^{-1}$ to a lower frequency for the *iso*cyanides. This result was confirmed by Badger and Bauer (*J. Amer. Chem. Soc.*, 1937, **59**, 303) in their examination of the absorption

FIG. 1.



(R = -C_6H_4·N:N·CN).

spectra of methyl cyanide and *iso*cyanide. Hibben (*op. cit.*, p. 280) has summarised the evidence obtained from numerous investigations of the Raman spectra of organic and inorganic cyanides and *iso*cyanides. Here, again, a similar shift of 100 cm.$^{-1}$ is obtained when comparing an *iso*cyanide with the corresponding cyanide. We would therefore expect that, if ν were the absorption frequency measured for any cyanide, where ν may lie roughly between the limits 2100—2250 cm.$^{-1}$ depending on the homopolar nature of the R–CN linking (Hibben, *op. cit.*, p. 454), the frequency would be approximately ν — 100 for the corresponding *iso*cyanide.

The spectra now recorded for methyl cyanide, *m*-tolyl cyanide, and phenyl cyanide show agreement with the frequency values obtained by previous authors. All pairs of diazocyanides examined have a common frequency, measured as 2160 cm.$^{-1}$.* This may be assigned to the

* The estimation of frequencies in the region 4·5 μ is not very precise when using a rock-salt prism and a cam which covers the whole spectral region 1—5 μ on a 12" photographic record. Since the measurements now recorded were completed, a special cam has been constructed which "spreads out" the spectrum in the region 4·5 μ, so that greater accuracy in frequency determination is possible. A value of 2187 cm.$^{-1}$ has now been obtained for the CN "stretching" frequency by a re-examination of the two forms of 4-bromobenzenediazocyanide. This is in excellent agreement with the value found by Sheppard and Sutherland (this vol., p. 453).

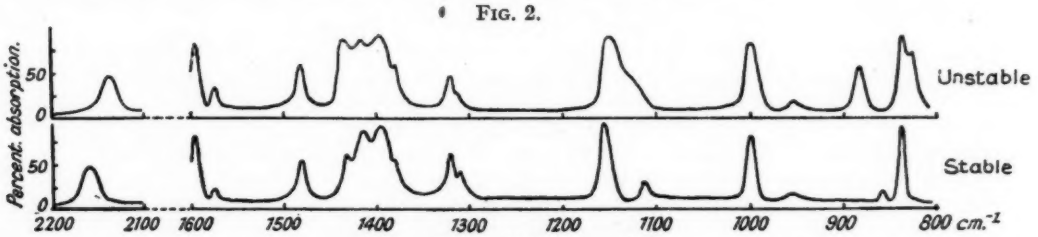
CN valency vibration. The important point is that there is no relative shifting of this frequency for any of the pairs now investigated—a fact which is substantially in favour of a cyanide form throughout.

Further evidence in support of this is the almost identical forms of the absorption spectra of any one pair of isomers in the range 1600—700 cm.$^{-1}$—where Badger and Bauer (*loc. cit.*) found distinct differences for methyl cyanide and *iso*cyanide (frequencies 1417, 1370, 1040, and 917 cm.$^{-1}$ for the cyanide, and 1456, 1414, 1041, and 928 cm.$^{-1}$ for the *iso*cyanide).

Barnes, Liddel, and Williams (*Ind. Eng. Chem.*, 1943, **15**, 659) summarise infra-red spectra of some 19 cyanides, including the following of interest to the present paper. Cyanamide and its allyl derivatives, *cis*- and *trans*-β-ethylacrylonitriles, and *cis*- and *trans*-crotononitriles all show strong absorption between 1400 and 1500 cm.$^{-1}$. Such bands are well known (compare Hibben, *op. cit.*, pp. 272, 294) to be associated with the CH and $-N{=}N-$ groups. The complexity observed is therefore reasonably to be expected.

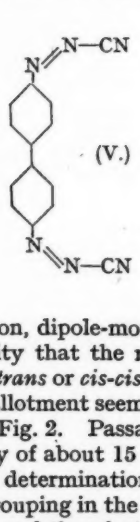
Before our spectrometer was available, specimens of the 2 : 4 : 6-tribromobenzenediazocyanides (provided by Dr. F. B. Kipping) and of the 4-bromobenzenediazocyanides (prepared by us) were kindly examined in chloroform, carbon disulphide, and nujol solutions by Dr. G. B. B. M. Sutherland on his double-beam instrument at Cambridge. His results are reported elsewhere (this vol., p. 453). They are in accord with our work in that the appropriate pairs show similarity, and other features, in satisfactory agreement with Figs. 1 and 2.

FIG. 2.

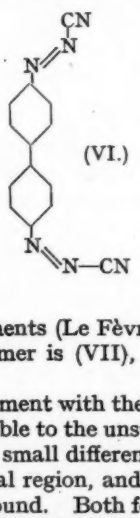


Diphenyl-4 : 4′-bisdiazocyanides.

Diphenyl-4 : 4′-bisdiazocyanides should occur as three isomerides, (V), (VI), and (VII), on Hantzsch's formulations. Only two forms, however, are known (Euler, *Chem. Zentr.*, 1907, i, 1572; Le Fèvre and Vine, *J.*, 1938, 1878). They differ in stability and other properties. Owing



(V.)



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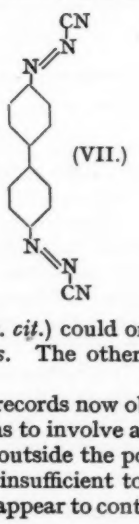


(VII.)

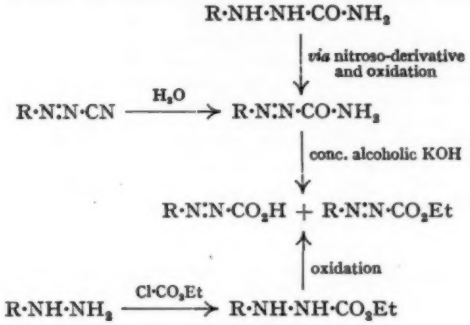
to free rotation, dipole-moment measurements (Le Fèvre and Vine, *loc. cit.*) could only indicate the probability that the more stable isomer is (VII), *i.e.*, *trans-trans*. The other, therefore, might be *cis-trans* or *cis-cis*.

Such an allotment seems to be in agreement with the spectroscopic records now obtained and presented in Fig. 2. Passage from the stable to the unstable form seems to involve a shift in the CN frequency of about 15 cm.$^{-1}$. Such a small difference is only just outside the possible error of frequency determination in this spectral region, and is in any case insufficient to suggest an *iso*cyanide grouping in the unstable compound. Both forms therefore appear to contain cyanide groups only, and thus further support the conclusions above.

Inspection of Figs. 1 and 2 reveals that all the molecules containing *syn*- (*cis*-) configurations about the $-N{=}N-$ group show a characteristic band system between the limits 800—900 cm.$^{-1}$, which does not occur with those possessing the *anti*- (*trans*-) arrangement. The curves of Fig. 2, by analogy, suggest that the stable diphenyl-4 : 4′-bisdiazocyanide does not contain a *cis*-azo-unit,

i.e., that it is correctly formulated as (VII). The unstable variety may, therefore, be either (V) or (VI). We have attempted to use the nearly quantitative precipitation of silver cyanide, noted by Stephenson and Waters (*loc. cit.*) as occurring between alcoholic solutions of *syn-* (not *anti-*) diazocyanides and silver nitrate, to effect a decision. The results (see Experimental) favour (V); (VI) is thus shown as the undiscovered member.

Summary.—From all the above physical considerations we conclude that in *syn-* and *anti-*diazocyanides the carbon and nitrogen atoms are *linked in the same manner*, most probably, as ·C⋮N. In case it might be urged that our work does not rigidly exclude the chance that the diazocyanides are geometrically isomeric *iso*cyanides, it should be mentioned that a number of reactions have been described in the literature from which the $^{-}$N, N, CN atomic sequence is *definitely* inferable, *e.g.*, the formation of imidocyanides and imidoethers with hydrogen cyanide and alcohols respectively, and of azo-carboxylic amides with water. Good examples (because they involve independent synthetic support) are the following (Widman, *Ber.*, 1895, **28**, 1925; Hantzsch and Schultze, *ibid.*, p. 670; Hantzsch and Danziger, *ibid.*, 1897, **30**, 2529):



Experimental.

Preparation of Diazocyanides.—The directions of Le Fèvre and Vine (*loc. cit.*) were used in the cases of the chloro-, bromo-, and nitro-derivatives. For the 4 : 4′-diphenylbisdiazocyanides the following improved method was adopted. Benzidine (10 g.), in a mixture of alcohol (25 c.c.) and 10N-hydrochloric acid (34 c.c.), was diazotised with sodium nitrite (7·8 g.) in water (125 c.c.) at 10°. The resulting solution was filtered, and chloroform (100 c.c.) added. To the mixture, cooled in an ice-bath, a solution of potassium cyanide (8 g.) in water (50 c.c.) was added dropwise with vigorous mechanical stirring. The temperature was maintained at 0°. The pale orange 4 : 4′-diphenylbisdiazocyanide was formed immediately, and rapidly dissolved in the chloroform. Stirring was continued for a further 15 minutes, and the two layers were then separated. The aqueous layer was extracted several times with 10-c.c. portions of chloroform, the extracts being added to the original chloroform portion. After being washed several times with distilled water, the chloroform extract was dried (Na_2SO_4), diluted to twice its volume with light petroleum (b. p. 40—60°), and cooled to 0°. Light orange micro-needles of the labile form of 4 : 4′-diphenylbisdiazocyanide then separated; these, after collection, washing (light petroleum), and drying in a vacuum desiccator in the dark, had m. p. (with explosion) 97—98°.

The stable form of 4 : 4′-diphenylbisdiazocyanide was formed gradually from the labile form on standing in the light at room temperature, but better by boiling a solution of the latter form in light petroleum (b. p. >120°). It was isolated as maroon-coloured crystals, m. p. (with explosion) 208—209°.

The diazocyanides used throughout the present work were examined with a polarising microscope and are specified in Table IV.

2 : 4-*Dinitrophenylhydrazones for comparison.* The compounds in Table V were prepared and characterised by means of m. p. and behaviour to polarised light.

Mixed M. ps.—The m. ps. of intimate mixtures of acetaldehyde and acetone 2 : 4-dinitrophenylhydrazones, made by grinding, were as follows:

CH_3·CHO deriv., %	0	10	20	30	40	50
M. p.	126°	115—117°	109—112°	108—110°	107—109°	108—110°
CH_3·CHO deriv., %	60	70	80	90	100	
M. p.	111—113°	120—123°	135—137°	150—152°	166°	

Interaction of Grignard Solutions with cis-*Diazocyanides.*—(a) *With* cis-p-*bromobenzenediazocyanide.* A large number of reactions were carried out using methylmagnesium iodide and phenylmagnesium bromide according to the directions of Hodgson and Marsden (*loc. cit.*). In some cases the 15 mins.' boiling (*idem, loc. cit.*, p. 398) was omitted, with the result that the yield of 2 : 4-dinitrophenylhydrazone was slightly increased, and the mixture appeared to be less complex, since its m. p. was higher than the product otherwise obtained. M. p.s of the products were taken as " crude ", after two recrystallisations from alcohol, and in admixture with authentic specimens of the dinitrophenylhydrazones of acetaldehyde

TABLE IV.

Diazocyanide.		M. p. (obs.).	M. p. (Le F. and V.).	Extinction angle.	Solvent.*	Description.
p-Cl·C_6H_4·N_2·CN	*cis*	29—30°	29°	*ca.* 46° to length of crystal	*Y* cooled on slide	Long thin parallelograms. Acute crystal angle *ca.* 45°
	trans	105	105	*ca.* 43° to length	*Z*	Thin parallelograms. Acute crystal angle *ca.* 51°
p-Br·C_6H_4·N_2·CN	*cis*	42—43	42—43	*ca.* 20° to length or straight extinction	*Y* cooled	Imperfect needles. Angles indefinite
	trans	132	132	*ca.* 22° to length.	*Z*	Thin parallelograms. Crystal angle *ca.* 63°
p-NO_2·C_6H_4·N_2·CN	*cis*	45—47	29—30	33° to length or straight extinction	*Y* cooled	Long thin needles. Angles indefinite
	trans	86	86	34° to length or straight extinction	*Z*	Imperfect needles (longer and thinner habit than *cis*-form)
(–C_6H_4·N_2·CN)$_2$	*labile*	97—98	97	All straight extinction	Pptd. from $CHCl_3$ with *Y*	Long imperfect needles. Angles indefinite
	stable	208—209	208	*ca.* 45° to length	*Z*	Long thin parallelograms. Crystal angle *ca.* 43°

* *Y* = Light petroleum, b. p. 40—60°. *Z* = Light petroleum, b. p. >120°.

TABLE V.

2 : 4-Dinitrophenylhydrazone of:	Solvent.	M. p. (obs.).	M. p. (lit.).*	Description.	Extinction.
Formaldehyde	EtOH	164—165°	166°	Long yellow needles and plates. Acute crystal angle *ca.* 60°	*Needles.* Straight extinction. *Plates.* *ca.* 37° to length
Acetaldehyde	,,	166	168	Long yellow rectangular plates	(1) Straight extinction or (2) *ca.* 42° to length
*iso*Valeraldehyde	,,	122—123	123	Crystallises from alcohol in two forms: (*a*) orange needles, (*b*) yellow plates	*Needles.* *ca.* 15° to length. *Plates.* *ca.* 25° to length
Acetone	,,	126	126	Yellow plates. Acute crystal angle 80°	*ca.* 30° to length
Mesityl oxide †	C_6H_6	202	203	Carmine, micro-crystals. Indefinite under microscope	—
Benzaldehyde	,,	236	237	Orange needles	Straight extinction

* Campbell (*Analyst*, 1936, **61**, 391).

† Included in case mesityl oxide were formed by the action of dil. H_2SO_4 on any acetone occurring in the aqueous extract from the reactions between MgMeI and *cis*-diazocyanides.

and acetone. In addition, the dinitrophenylhydrazones were examined under the polarising microscope after recrystallisation. In general, they appeared to be mixtures of acetaldehyde and acetone dinitrophenylhydrazones. The usual m. p. obtained for the crude product was about 140—145°, which corresponded to between 80 and 85% of acetaldehyde in the mixtures. In one case (see Table VI), acetone 2 : 4-dinitrophenylhydrazone was obtained as a single substance. The traces of dinitrophenylhydrazone obtained from the reactions with phenylmagnesium bromide were too small to demonstrate the presence of the derivative of benzaldehyde. Our observations suggested that the acetaldehyde derivative was largely produced (see Table VI).

Table VI summarises typical results obtained from various reactions with *cis*-*p*-bromobenzenediazocyanide (0·01 g.-mol. used throughout).

(b) *With the labile form of* 4 : 4′-*diphenylbisdiazocyanide.* An ethereal solution of this labile form (0·01 g.-mol.) was added slowly to methylmagnesium iodide (0·02 g.-mol.) in ether at 0°. A dark blue complex was formed immediately, which turned brown on decomposition with iced 2N-sulphuric acid. The aqueous layer was separated, filtered, and treated with 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid. The resulting dinitrophenylhydrazone (0·5 g.) was filtered off, recrystallised twice from alcohol,

TABLE VI.

Grignard reagent.	Wt. (g.) and m. p. of crude dinitrophenylhydrazone.	M. p. after 2 recrystallisations from EtOH.	Mixed m. p. with acetaldehyde deriv.	Mixed m. p. with acetone deriv.	Appearance under polarising microscope, and extinction angle.
MgMeI	0·4; 135—137°	148—149°	149—150°	122—126°	Long, yellow, rectangular plates. Straight extinction
MgMeI	0·3; 112—115	125 †	114	125	Yellow plates. Acute crystal angle *ca.* 80°. Extinction: 30° to length
MgMeI	0·34; 140—141	161—162	162	140—142	Long, rectangular plates Straight extinction
MgMeI *	0·45; 140—143	161—162	162—163	132—135	,, ,, ,,
MgPhBr	0·10; 138—140	155—156	157—159	—	,, ,, ,,
MgPhBr * ...	0·15; 142—145	157—159	158—159	—	,, ,, ,,

* 15 Mins.' boiling omitted. † After 4 recrystallisations.

and examined under the polarising microscope. The crude product had m. p. 143—145°, raised after two recrystallisations to 148—150°. This, mixed with acetaldehyde dinitrophenylhydrazone, had m. p. 154—157°, and with the acetone derivative, 104—106°. Two varieties of crystals occurred, some with straight extinction and others with extinction at 40° to length (cf. acetaldehyde in Table V).

(c) *Reactions with methylmagnesium iodide in* iso*amyl ether and anisole.* The directions of Hodgson and Marsden (*loc. cit.*) were followed, solutions of methylmagnesium iodide and *cis-p*-bromobenzenediazocyanide in both *iso*amyl ether and anisole instead of ethyl ether being used. Orange-red complexes were again formed, and decomposed with iced 2N-sulphuric acid. On treating the aqueous extracts with 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid, no dinitrophenylhydrazone was formed. The ethereal layer from the reaction in *iso*amyl ether was distilled, and the first c.c. of the distillate was shaken with a solution of 2 : 4-dinitrophenylhydrazine in 2N-sulphuric acid. An orange precipitate was slowly formed. This was filtered off, recrystallised from alcohol, and examined as before. Distillation of the anisole layer produced no precipitate with 2 : 4-dinitrophenylhydrazine. The m. p. of the crude derivative was 85—89°, raised, after two recrystallisations, to 110—120°. The mixed m. p. with the acetaldehyde hydrazone was 98—102°, and that with the *iso*valeraldehyde derivative, 115—118°. The extinction angle was *ca.* 15° to the length (see Table V).

It thus appears that the dinitrophenylhydrazone obtained from the reaction in *iso*amyl ether is *not* the acetaldehyde derivative but mainly that of *iso*valeraldehyde. This is consistent with the view that the aldehydes produced arise either from the oxidation of the ether by the *cis*-compounds or from free radicals occurring in the ethereal solutions. The failure of the anisole solutions to produce any phenylhydrazone-forming product is not significant since oxidation of anisole would produce formaldehyde which would be too volatile for isolation and identification.

Estimation of Silver Cyanide produced from the Labile Form of 4 : 4′*-Diphenylbisdiazocyanide by Alcoholic Silver Nitrate.*—The labile form of the cyanide (0·036 g.) in a mixture of redistilled chloroform (20 c.c.) and absolute alcohol (80 c.c.) was added to an alcoholic solution of silver nitrate (1 g. in 25 c.c. of 80% alcohol). The precipitated silver cyanide was filtered off, washed successively with water, alcohol, and chloroform, dried and weighed. Yield 0·036 g., *i.e.*, 97% based on a *cis–cis*-configuration.

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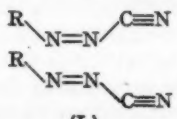
90. *The Infra-red Spectra and Molecular Structure of Certain Isomeric Diazocyanides.*

By N. SHEPPARD and G. B. B. M. SUTHERLAND.

An investigation of the vibration spectra of certain isomeric diazocyanides of the Hantzsch type proves conclusively that these isomers cannot be related as cyanide and *iso*cyanide but are both cyanides.

THERE has been some controversy recently over the structure of Hantzsch's *syn-* and *anti*-diazocyanides. It was suggested by Hodgson and Marsden (*J.*, 1944, 395) that these



(I.)

R—N=N—CN

R—N=N—NC

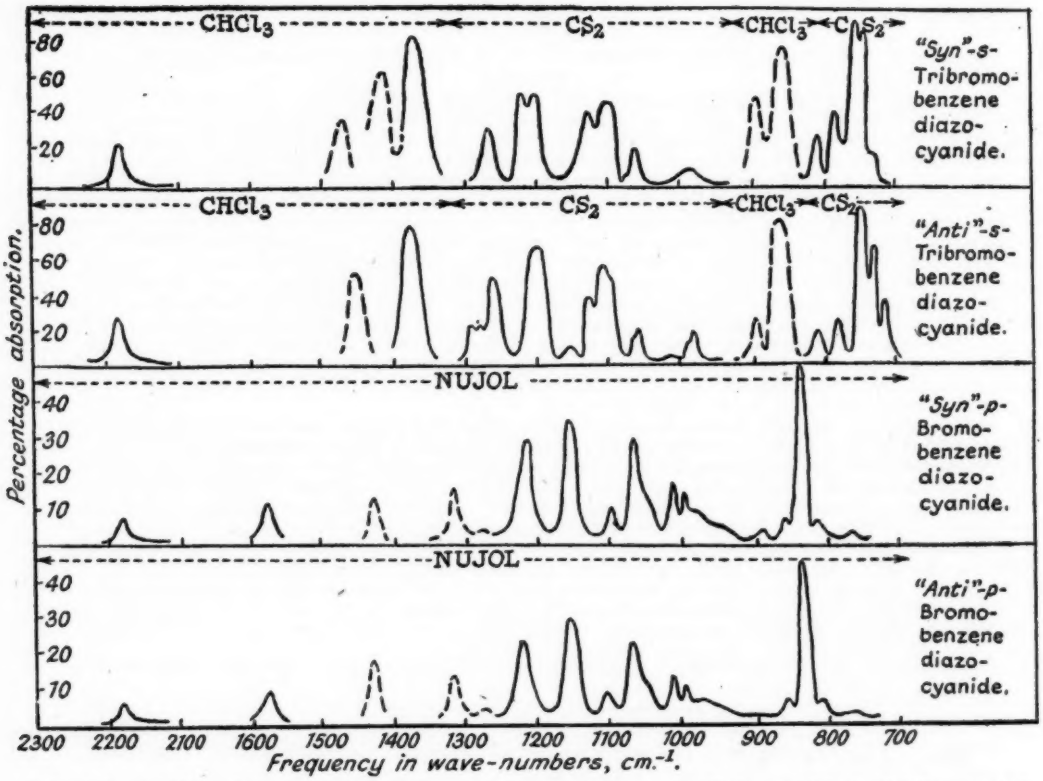
(II.)

compounds are not *syn-* and *anti*-isomers (I), but cyanides and *iso*cyanides (II), but Le Fèvre and Vine (*J.*, 1938, 431) maintained that studies on dipole moments confirm Hantzsch's original

hypothesis. The work now described arose from a query by Dr. Le Fèvre whether infra-red spectroscopy could throw any further light on this structural problem.

Experimental.

The compounds examined were the two 2 : 4 : 6-tribromobenzenediazocyanides (prepared by Dr. F. B. Kipping) and the two 4-bromobenzenediazocyanides (prepared by Mr. D. Anderson). The spectra of all four compounds have been investigated in the infra-red between 2 μ (5000 cm.$^{-1}$) and 15 μ (667 cm.$^{-1}$), a double-beam infra-red prism spectrometer being used (Sutherland and Thompson, *Trans. Faraday Soc.*, 1945, **41**, 174). The tribromo-compounds were examined in solution, and the monobromo-derivatives as a paste in "Nujol". A rock-salt prism was used as the dispersing agent over the whole range, but in addition the bands near 2200 cm.$^{-1}$ were re-examined on a Hilger D88 spectrometer, a lithium fluoride prism being used to get greater precision in the determination of the position of a critical band which lies in this region. The exact position was determined by comparison



Infra-red absorption spectra of the stable ("anti") *and unstable* ("syn") *forms of* 2 : 4 : 6-*tribromo- and* 4-*bromo-benzenediazocyanides. The tribromo-compounds were in solution* (10% *in* $CHCl_3$ *or* 7% *in* CS_2 *in the regions indicated*) ; *the monobromo-compounds were in a Nujol paste.*

with a band due to gaseous carbon disulphide which lies at 2184 cm.$^{-1}$ (Sanderson, *Physical Rev.*, 1935, **50**, 209). The spectra are given in the figure. The solvents were chloroform and carbon disulphide, an approximately 10% solution being used in each case. These solvents have absorption bands in the infra-red which interfere slightly with the determination of parts of the spectrum but not in a critical region. A few bands, the intensities of which are less certain on account of this interference, have been indicated by broken lines. Similarly, in the case of the spectra taken in Nujol, the bands between 1250 and 1450 cm.$^{-1}$ are less certain because of the characteristic hydrocarbon bands due to Nujol at 1450 and 1370 cm.$^{-1}$.

Discussion.*

It has been shown by several workers that cyanides can be very readily distinguished from the corresponding *iso*cyanides by their vibration spectra. For instance, Gordy and Williams (*J. Chem. Physics*, 1936, **4**, 85) examined methyl, ethyl, butyl, and phenyl cyanides and the

* The different types of CN frequency are indicated by the symbols –CN (cyanide) and –NC (*iso*cyanide). Where it is not possible to distinguish between the two the symbol CN is used.

corresponding *iso*cyanides in the infra-red between 2·9 μ (3450 cm.$^{-1}$) and 5·0 μ (2000 cm.$^{-1}$) in order to study the variation in the position of the absorption frequency corresponding to the CN stretching vibration. Their results are summarised in Table I, where we have also given the

TABLE I

CN *Frequencies in cyanides and* isocyanides.

	Infra-red data, in cm.$^{-1}$.	Δν.	Raman data, in cm.$^{-1}$.	Δν.
Methyl cyanide	2283	100	2250	89
,, *iso*cyanide	2183		2161	
Ethyl cyanide	2257	97	2246	100
,, *iso*cyanide	2160		2146	
Butyl cyanide	2247	96	—	—
,, *iso*cyanide	2151		—	
Phenyl cyanide	2232	109	2232	—
,, *iso*cyanide	2123		—	

earlier Raman data due to Dadieu and Kohlrausch (*Wien. Ber.*, 1930, **139**, 165), Bhagavantam (*Indian J. Physics*, 1930, **5**, 48), and Petrikaln and Hochberg (*Z. physikal. Chem.*, 1930, **8**, *B*, 440). It was Dadieu and Kohlrausch (*loc. cit.*) who first pointed out that the CN frequency differed by about 100 cm.$^{-1}$ in going from a cyanide to the corresponding *iso*cyanide. Table I shows that this was amply confirmed by Gordy and Williams. The latter workers, however, remarked another important difference between the CN frequency in such isomers. It is that the −NC absorption frequency in the *iso*cyanides is almost exactly twice as intense in absorption as the −CN frequency in the cyanides.

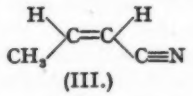
If, therefore, the pairs of isomers we examined were related as cyanides and isocyanides, we should expect the CN frequency to differ in value by about 100 cm.$^{-1}$ and in intensity by a factor of 2 between the members of each pair. Instead, we find there is no difference either in position or in intensity between the CN frequency in the isomers. The exact values observed by us were as follows

2 : 4 : 6-Tribromo- (stable derivative) 2185 4-Bromo- (stable derivative) 2185

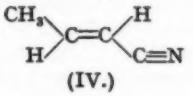
2 : 4 : 6-Tribromo- (unstable derivative) 2187 4-Bromo- (unstable derivative) 2185

These values are correct to ± 5 cm.$^{-1}$. *This proves conclusively that these compounds are not structural isomers of the cyanide–isocyanide type.* It remains to be decided whether the spectroscopic results allow one to make further deductions on their structure.

The vibration spectra of a few *cis*- and *trans*-isomers containing a CN bond have been determined. De Hemptinne and Wouters (*Ann. Soc. Bruxelles*, 1933, **53**, *B*, 215) examined the Raman spectra of *cis*- and *trans*-crotononitrile, (III) and (IV). They found the CN frequency



(III.)



(IV.)

to have the value 2235 cm.$^{-1}$ in the *trans*- and 2226 cm.$^{-1}$ in the *cis*-form, *i.e.*, a difference of less than 10 cm.$^{-1}$. The same two compounds were examined later by Reitz and Sabbathy (*Monatsh.*, 1938, **71**, 131) in what appears to be a more careful investigation. They obtained values for the CN frequency of 2217 cm.$^{-1}$ and 2220 cm.$^{-1}$, respectively, in the *cis*- and *trans*-forms, *i.e.*, a difference of only 3 cm.$^{-1}$. We may therefore conclude from the fact that each pair of our "diazocyanides" gives the CN frequency in the same position to within 10 cm.$^{-1}$, that this is strong evidence that each pair consists of a *cis*- and a *trans*-form of either a cyanide or an *iso*cyanide.

The question whether the compounds are all cyanides or all *iso*cyanides is harder to decide. It will be noticed that the CN frequency in the "diazocyanides" (2185 cm.$^{-1}$) occupies an intermediate position between the −CN frequency of the cyanides and the −NC frequency of the *iso*cyanides in Table I, the former ranging between 2283 and 2232 cm.$^{-1}$ while the latter vary between 2183 and 2123 cm.$^{-1}$. If, then, the "diazocyanides" are cyanides, there must be some reason for the abnormally low value of their −CN frequency, while if they are *iso*cyanides an explanation must be found for the increase in the −NC frequency.

Let us first examine the causes of the variations in the −CN frequency of the cyanides, summarised in Table II. This frequency decreases steadily in going from methyl cyanide

TABLE II.

Variations in the −CN *Frequency in Cyanides.*

(1) "Mass" effect.

	cm.$^{-1}$.
$CH_3 \cdot CN$	2283
$C_2H_5 \cdot CN$	2257
$C_3H_7 \cdot CN$	2247
$C_4H_9 \cdot CN$	2245
$C_5H_{11} \cdot CN$	2241

(2) Conjugation effect.

	cm.$^{-1}$.	$\Delta\nu$.
$Ph \cdot CH_2 \cdot CN$	2273	41
$Ph \cdot CN$	2232	
$CH_3 \cdot CH_2 \cdot CN$	2257	
$CH_2(CN) \cdot CH_2 \cdot CN$	2254	
$CH_2 \cdot CH \cdot CN$	2224	35 mean
$CH_2 \cdot CMe \cdot CN$	2224	
cis-$CH_3 \cdot CH \cdot CH \cdot CN$	2217	
trans-$CH_3 \cdot CH \cdot CH \cdot CN$	2220	
$CMe_2 \cdot CH \cdot CN$	2216	

(2283 cm.$^{-1}$) to amyl cyanide (2241 cm.$^{-1}$). This is partially a mass effect and we may reasonably assume that, on this account in the large diazocyanides under discussion here, the −CN frequency should be at the lower end of its range, *i.e.*, near 2250 cm.$^{-1}$. There is next the effect of conjugation on the −CN frequency, which is illustrated by section (2) of Table II. It will be observed that in analogous molecules conjugation of the C≡N bond to a C=C bond causes a lowering of the −CN frequency by 35—40 cm.$^{-1}$. In the diazocyanides the C≡N bond will be conjugated to an N=N bond. Unfortunately, no spectroscopic data exist on the effect of this type of conjugation on the CN frequency but it would be expected to be very similar to conjugation with a C=C bond. On these grounds we may expect to find the −CN frequency abnormally low in diazocyanides for two independent reasons, and quantitatively the effects are of the right order to make the −CN frequency in diazocyanides about 2200 cm.$^{-1}$ or even slightly lower.

Let us next consider variations in the −NC frequency in the *iso*cyanides (Table III). The

TABLE III.

Variations in the −NC *frequency in* isocyanides.

(*a*) "Mass" effect.

	cm.$^{-1}$.
$CH_3 \cdot NC$	2183
$C_2H_5 \cdot NC$	2160
$C_3H_7 \cdot NC$	2151

(*b*) Conjugation effect.

	cm.$^{-1}$.	$\Delta\nu$.
$C_3H_7 \cdot NC$	2151	28
$Ph \cdot NC$	2123	

same "mass" effect is observed as in the cyanides and so on this account one would expect the −NC frequency in a diaz*oiso*cyanide of the size we are considering to lie around 2150 cm.$^{-1}$. Unfortunately, no analogues have been examined for the conjugation effect, but the fact that it must exist is clear from the comparison of the value of the −NC frequency in butyl and phenyl *iso*cyanide in section (*b*) of Table III. On the same grounds then that we predicted a value of about 2200 cm.$^{-1}$ for the −CN frequency in a large conjugated diazocyanide, we should predict a value of about 2100 cm.$^{-1}$ for the −NC frequency in a similar diaz*oiso*cyanide. The observed value of 2185 cm.$^{-1}$ in the four compounds examined by us is therefore strong evidence that these compounds are all diazocyanides and not diaz*oiso*cyanides.

The discussion of the other evidence in favour of regarding these compounds as *syn*- and *anti*-diazocyanides is given in the preceding paper by Anderson, Le Fèvre, and Savage. These authors have also examined the infra-red spectra of *syn*- and *anti*-*p*-chloro-, -*p*-bromo-, -*p*-nitro-, and -2 : 4 : 6-tribromo-benzenediazocyanides and two of the diphenyl-4 : 4′-bisdiazocyanides. Their results confirm our observations on the *p*-bromo-compounds. Furthermore they find the CN frequency to be in exactly the same position (2185 cm.$^{-1}$) in all their other diazocyanides. The spectroscopic evidence against the *iso*cyanide theory can therefore be regarded as overwhelming.

We wish to express our thanks to Dr. R. J. W. Le Fèvre for drawing our attention to this problem and to Dr. F. B. Kipping for preparing the 2 : 4 : 6-tribromobenzenediazocyanides.

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91. *Magnetic Optical Rotatory Powers and Diamagnetic Susceptibilities of the Isomeric Aromatic Diazocyanides.*

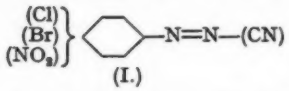
By D. Anderson, (Miss) M. E. Bedwell, and R. J. W. Le Fèvre.

The above properties have been examined, respectively, in solution and in the solid state, for the isomeric pairs of *p*-chloro-, *p*-bromo-, and *p*-nitro-benzenediazocyanides, together with the two known forms of 4 : 4′-diphenylbisdiazocyanide.

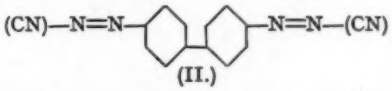
The results agree more closely with expectations based on a geometrical (*cis–trans*-cyanide) relationship (Hantzsch) than with those on a structural (*iso*cyanide–cyanide) relationship (Orton; Hodgson and Marsden).

Recently (this vol., p. 445) Anderson, Le Fèvre, and Savage discussed the structures of the isomeric aromatic diazocyanides, deciding that they were better represented as pairs of cyanides having a *cis–trans*-relationship, than as *iso*cyanides and cyanides (both *trans*), respectively; *i.e.*, the "classical" explanation of Hantzsch was preferred to the later one of Orton and of Hodgson and Marsden (see above).

To the evidence previously considered we now add that obtained by an examination of the magnetic optical rotating powers in benzene solution, and the diamagnetic susceptibilities in the solid state, of the eight compounds corresponding to the formulæ (I) and (II).



(I.)



(II.)

At the outset, data, from which we might argue by analogy, showing the direction or degree of difference in these properties likely to be caused by the change of R–C≡N into R–$\overset{+}{\text{N}}\equiv\overset{-}{\text{C}}$, did not appear to be available in the literature. Fortunately, however, methods by which they could be deduced *a priori* had been described. We therefore have used these and compared our experimental observations with the results.

Magnetic Optical Rotatory Powers.—Becquerel (*Compt. rend.*, 1897, **125**, 679) has shown that the magneto-rotatory power, θ, of a substance is connected *inter alia* with its refractive index, *n*. His conclusions can be written (Bhatnagar and Mathur, "Physical Principles and Applications of Magneto Chemistry") in the form

$$\theta = \frac{l\lambda He}{2mc} \cdot \frac{dn}{d\lambda}$$

where H is the field, λ the wave-length of the light used, l the optical path thickness through the material, c the velocity of light, and e and m the electronic charge and mass respectively.

Accordingly, for a given λ, and otherwise unaltered experimental conditions, the θ values for two isomers will differ if their $dn/d\lambda$ coefficients differ; further, the relative magnitudes of the θ's will also follow. For the present enquiry, therefore, the refractive indices recorded by von Auwers (*Ber.*, 1927, **60**, 2122) are relevant. In Table I we have listed appropriate data,

Table I.

Substance.	*t*.	$n^{t°}_{\alpha}$.	$n^{t°}_{\beta}$.	$n^{t°}_{\gamma}$.	$n^{t°}_{\gamma} - n^{t°}_{\alpha}$.	$n^{t°}_{\beta} - n^{t°}_{\alpha}$.
Me·NC	17·9°	1·34186	—	1·35326	0·01140	—
Et·NC	17·6	1·36124	—	1·37275	0·01151	—
C_6H_5·NC	18·1	1·52240	1·54207	—	—	0·01967
Me·CN	21·9	1·34008	—	1·34943	0·00935	—
Et·CN	21·8	1·36182	—	1·37185	0·01003	—
C_6H_5·CN	25·5 *	1·52035	1·53942	—	—	0·01907

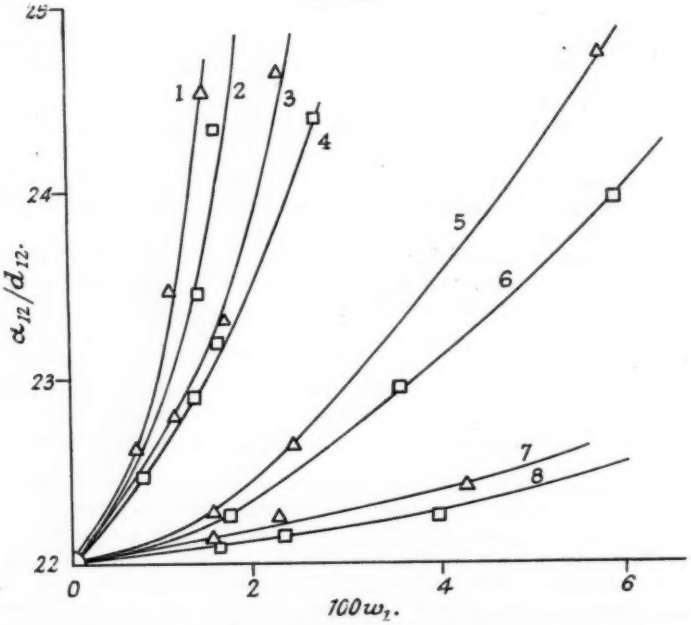
* Data from Landolt–Börnstein "Tabellen".

from which it is clear that $dn/d\lambda$ for an *iso*cyanide is greater than for the corresponding cyanide. At equivalent concentrations, therefore, the magnetic rotations of solutions of the isomeric diazocyanides should display inequalities in the same sense *if* the unstable and stable forms differ only in being *iso*- and normal cyanides.

Fig. 1 has been drawn from the measurements recorded in Table III. It will be seen that for all four cases studied the magnetic rotation of the stable form is *higher* than that of the unstable. The suggestion that the latter series are *iso*cyanides is therefore disfavoured.

Since, however, in general, among authentic geometrical pairs, θ_{trans} is greater than θ_{cis} (*e.g.*, the molecular magneto-optic rotations of ethyl fumarate and maleate are 10·1 and 9·6; Perkin, *J.*, 1896, **69**, 1236), our measurements would be in harmony with the original relationship proposed by Hantzsch, based on geometrical isomerism, in which *all* the forms contain cyanide groups.

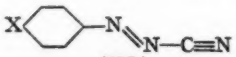
FIG. 1.



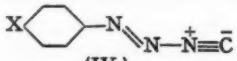
Magneto-optic rotation of the isomeric diazocyanides in benzene solution.

1. trans-p-*Nitrobenzenediazocyanide.*
2. cis-p-*Nitrobenzenediazocyanide.*
3. trans-p-*Chlorobenzenediazocyanide.*
4. cis-p-*Chlorobenzenediazocyanide.*
5. trans-p-*Bromobenzenediazocyanide.*
6. cis-p-*Bromobenzenediazocyanide.*
7. *Stable form of* 4 : 4′-*diphenylbisdiazocyanide.*
8. *Labile form of* 4 : 4′-*diphenylbisdiazocyanide.*

Diamagnetic Susceptibilities.—The "experimental molecular standards" for the two structures (III) and (IV) (X = Cl, Br, or NO_2) have been estimated by the method described



(III.)



(IV.)

by Gray and Cruikshank (*Trans. Faraday Soc.*, 1935, **31**, 1491). This requires a deduction of the "theoretical molecular standards" from figures for the constituent atoms (Pauling, *Proc. Roy. Soc.*, 1927, **114**, 181), account being taken of the residual charges due to the unequal sharing of bond electrons (Sidgwick, "The Covalent Link in Chemistry," Cornell Univ. Press), followed by a correcting subtraction for the depressions of diamagnetism (Gray and Cruikshank, *loc. cit.*) which occur on bond formation. "Experimental molecular standards" result; *i.e.*, Exptl. mol. std. = Theor. mol. std.—Σ Bond depressions. These are the quantities which could be expected from practical measurements, were the actual structures initially assumed truly present. In Table II our experimental observations are compared with the results of calculation.

The results indicate that the stable and the unstable form of each compound are unlikely to be related as cyanide and *iso*cyanide respectively. In every case the unstable form is seen to have only a slightly higher susceptibility than the stable form. This is not incompatible with a *cis–trans*-relationship, Bhatnagar, Mathur, and Nevgi (*Z. Physik*, 1931, **69**, 373) having found *e.g.*, that maleic and fumaric acids have about the same order of difference (maleic acid, $-\chi_M \times 10^6 = 49{\cdot}71$; fumaric acid, $-\chi_M \times 10^6 = 49{\cdot}11$).

TABLE II.

Diazocyanide.	Theor. mol. std. Structure. (III).	Theor. mol. std. Structure. (IV).	Bond depression. Structure. (III).	Bond depression. Structure. (IV).	"Corr. mol. std." (G. and C.). Structure. (III).	"Corr. mol. std." (G. and C.). Structure. (IV).	Expt. mol. diam. (obs.). Unstable form.	Expt. mol. diam. (obs.). Stable form.
Chlorobenzene	125·17	127·14	58·55	65·17	66·62	61·97	65·81	65·02
Bromobenzene	148·07	150·04	59·22	65·84	88·85	84·20	87·46	86·88
Nitrobenzene	136·98	138·95	75·64	82·26	61·34	56·67	59·90	59·22
Diphenylbis	206·96	210·90	118·92	132·16	88·04	78·74	86·89	85·03

Basic data for the constituent groups:

Group.	Theor. mol. std.	Bond depression.	"Exptl. mol. std."
C—Cl	31·23	0·08, calc. from CH_3Cl by Gray and Cruikshank's method	31·15
C—Br	54·11	0·75, calc. from CH_3Br by Gray and Cruikshank's method	53·36
N—N	16·56	2·13, by analogy, from C—C, N—H, C—H	14·43
N=N	16·56	12·85, by analogy, from C=O, N=O, C=C	4·71
C—NO_2	43·02	16·20	26·82
C_6H_4	61·81	37·62	24·19
C—N=N—C≡N ...	32·15	21·91	10·24
C—N=N—$\overset{+}{N}\equiv\overset{-}{C}$ ...	34·10	27·17	6·93

Method of calculation (*e.g.*, for C_6H_4):

C	6 × 0·04 × 14·69	53·08
	6 × 0·96 × 8·60	
H	4 × 0·04 × 0	8·73
	4 × 0·96 × 2·273	
∴ Theor. mol. std. (C_6H_4)		61·81

Bond depressions	3C=C	28·5
	3C—C	5·94
	6C—H	3·18
∴ Bond depressions (C_6H_4) ...		37·62
∴ "Expt. mol. std."		24·19

EXPERIMENTAL.

Measurement of Magneto-optic Rotations.—The apparatus was based on that used by Roger and Watson (*Proc. Roy. Soc.*, 1895, *A*, **58**, 234; *Phil. Trans.*, 1895, **186**, 654) and Bhatnagar, Mathur, and Jain (*Ind. J. Physics*, 1930, **4**, 503), in which the field was produced within a solenoid. The latter was wound on a brass former, and the ends of the polarimeter tube were fitted with aluminium friction-tight rings which slid easily inside, thus providing a centring device. A brass pin projecting from the inner wall ensured that the tube could always be replaced in the region of uniform field towards the centre of the solenoid (Fig. 2). The coil was supported by square end-plates standing in grooves along which it could be slid laterally to allow withdrawal of the polarimeter tube.

The field inside the solenoid, ascertained by means of a search coil, was found to be reproducibly fixed at 3880 gauss by always adjusting the current in *A* to read 15 amps. All measurements were conducted in benzene solution at 25°.

The results are shown in Table III. w_1 is the weight fraction of the solute in each solution, and d_{12} and α_{12} are respectively the density and rotation.

TABLE III.

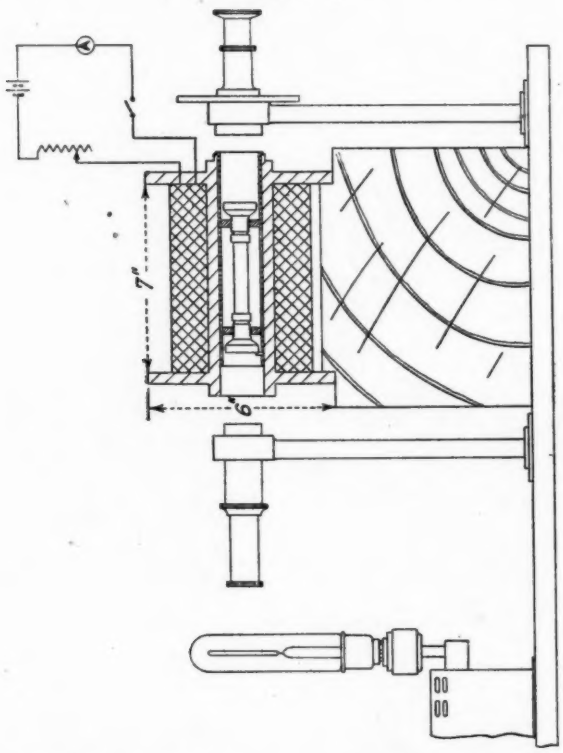
$100\,w_1$.	$(d_{12})^{25°}_{4°}$.	α_{12}.	α_{12}/d_{12}.	$100\,w_1$.	$(d_{12})^{25°}_{4°}$.	α_{12}.	α_{12}/d_{12}.
0	0·87255	19·2	22·01				
cis-p-*Nitrobenzenediazocyanide.*				cis-p-*Bromobenzenediazocyanide.*			
0·7820	0·87641	19·7	22·48	1·735	0·88136	19·6	22·24
1·437	0·87834	20·6	23·46	3·601	0·88878	20·4	22·95
1·603	0·87879	21·4	24·35	5·898	0·89699	21·5	23·96
trans-p-*Nitrobenzenediazocyanide.*				trans-p-*Bromobenzenediazocyanide.*			
0·7710	0·87516	19·8	22·62	1·597	0·88021	19·6	22·27
1·1470	0·87734	20·6	23·48	2·466	0·88346	20·0	22·63
1·5260	0·87855	21·6	24·59	5·847	0·89754	22·2	24·74
cis-p-*Chlorobenzenediazocyanide.*				*Unstable* p-*diphenyldiazocyanide.*			
1·385	0·87770	20·1	22·9	1·606	0·87804	19·4	22·08
1·821	0·87895	20·4	23·2	2·304	0·88043	19·5	22·12
2·555	0·88099	21·5	24·4	4·003	0·88604	19·7	22·24
trans-p-*Chlorobenzenediazocyanide.*				*Stable* p-*diphenyldiazocyanide.*			
1·154	0·87704	20·0	22·80	1·581	0·87839	19·4	22·09
1·734	0·87876	20·5	23·33	2·264	0·88081	19·6	22·25
2·338	0·88047	21·7	24·65	4·299	0·88831	19·9	22·41

Measurement of Magnetic Susceptibility.—The modified Gouy method of measurement was employed (*Compt. rend.*, 1889, **109**, 935; Trew and Watkins, *Trans. Faraday Soc.*, 1933, **30**, 1310; Angus and Hill, *ibid.*, 1943, **39**, 185), a field of 10,000 gauss being used and a pole gap of 2·0 cm. with a current of 12 amps. at 220 volts D.C. Sensible heating of the coils did not occur during the course of experiments. In order to prevent damage by the initial surge of current when contact was made or broken, the circuit included a voltage limiting resistance and a d. p. contactor, which were on a switchboard remote from the Gouy balance. The d. p. contactor was operated by a pole-switch on the balance table.

The field was measured by means of a Grassot fluxmeter and search coil, but the balance constant was determined by measurements on a column of pure acetone.

All measurements were made at 20°. The molar susceptibilities were calculated from the expressions $\chi_M = M \times \chi_g$ and $10^6 \chi_g = (aF + 0{\cdot}0294V)/W$, where χ_M and χ_g are the molar and specific susceptibilities, M is the molecular weight of the substance, a the balance constant, F the pull on the substance due to the magnetic field, V the volume of the column of the substance (equal to the volume of acetone used in calibration), and W the weight of the substance employed.

FIG. 2.



The susceptibility of acetone was taken to be $\chi_{acetone} = -0{\cdot}5866 \times 10^{-6}$ (French and Trew, *Trans. Faraday Soc.*, 1945, **41**, 442).

The results are shown in Table II.

Preparation of Diazocyanides.—By the following modification of the directions of Le Fèvre and Vine (*J.*, 1938, 431, 1878) greatly improved specimens of unstable forms are obtained: The amine (0·1 mol.) in concentrated hydrochloric acid (45 c.c.) and water (45 c.c.) is diazotised (sodium nitrite, 6·9 g.; water, 50 c.c.). The filtered solution, plus alcohol (50 c.c.), is cooled to −25° (EtOH–CO_2), and stirred almost to an emulsion with light petroleum (b. p. 40—60°; 200 c.c.) under careful exclusion of light. Potassium cyanide (13 g.) in water (50 c.c.) is then added dropwise. Stirring is continued while the mixture warms to 0°. The hydrocarbon layer is separated, dried (Na_2SO_4), and cooled in the dark to −30°. Rapid filtration (dry air), followed by storage at 0° in an opaque vacuum desiccator, then provides, without further purification, materials with m. p.s as high as ever previously recorded (yields *ca.* 0·025 mol.). From the mother-liquor, stable forms are obtained by concentration at the b. p., followed by cooling, etc.

ROYAL AIRCRAFT ESTABLISHMENT, SOUTH FARNBOROUGH, HANTS. [*Received, July 22nd*, 1946.]

92. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XIX. Derivatives of 4′-Nitro-2′-methoxybenzene-2-naphthol-1-diazosulphonate.*

By (the late) F. M. Rowe and E. J. Cross.

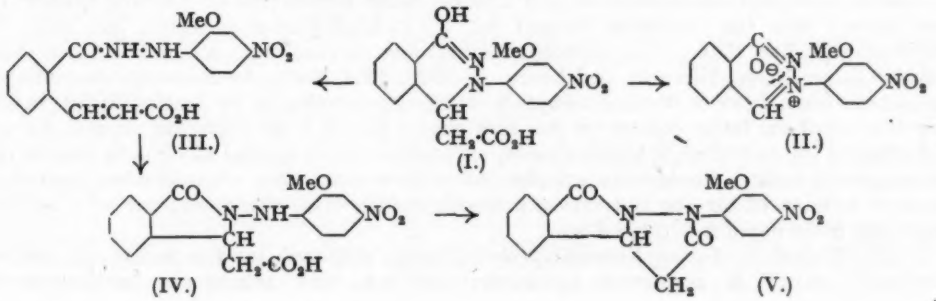
Although the reactions and the properties of the products in the present series in general approximated to those recorded for analogous compounds containing the nitro- or amino-group in the 4′-position, some interesting differences have been found. The methoxyl group is more stable than the phthalazine ring under demethylating conditions, and the corresponding hydroxy-compound could not be prepared from 1-*hydroxy*-3-(4′-*nitro*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (I). Attempted demethylation of (I) with fuming hydrochloric acid at 180° gave 4′-*nitro*-2′-*methoxy*-3-*phenylphthalaz*-1-*one* (II) and 2-(4′-*nitro*-2′-*methoxyphenylamino*)iso*indolinone*-3-*acetic acid* (IV). Both (II) and (IV) are also formed by refluxing (I) with aqueous sulphuric acid. Compound (IV) must be formed from (I) by opening of the phthalazine ring to benzo-4′-nitro-2′-methoxyphenylhydrazide-2-β-acrylic acid (III), followed by closure under the acid conditions to the 5-membered ring compound (IV). Compound (IV) is the first example of a compound of this type with a nitro-group in the 4′-position, as hitherto analogues have only been obtained with the nitro-group in the 2′-position. Rapid acidification of sodium 1-(4′-nitro-2′-methoxybenzeneazo)-β-naphthaquinone-1-sulphonate in sodium hydroxide and boiling the product with dilute hydrochloric acid gave a mixture of (I) and (IV). Conversion of the alcohol compounds of methylated bases from 4′- or 3′-nitro-3-phenylphthalaz-1-one into 4-keto-1-methoxy-3-(4′- or 3′-nitrophenyl)-3 : 4-dihydrophthalazine by heating has been found to be an oxidation process. 1-*Hydroxy*-3-(4′-*amino*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* behaves in an unusual manner when boiled with mineral acid for, although the anticipated 4′-*amino*-2′-*methoxy*-3-*phenylphthalaz*-1-*one* (VIII; R = H) is formed, the main product is its 4-methyl derivative (VIII; R = Me), decarboxylation occurring preferentially to the elimination of acetic acid.

The preparation of phthalazine derivatives from 2-halogeno- and 2 : 6-dihalogeno-4-nitroanilines and from 5-nitro-*o*-toluidine has already been described (Rowe *et al.*, *J.*, 1931, 1073; 1932, 11, 473; 1935, 1134). In extending the series, it was desired to include a 2-hydroxy-nitroamine, but attempts to produce phthalazine derivatives from 4-nitro-2-aminophenol were unsuccessful. Phthalazine compounds were therefore prepared from 5-nitro-2-anisidine with a view to subsequent conversion into the 2′-hydroxy-derivatives by demethylation, and in order to determine the influence of the methoxyl groups on the course of the reaction and its products.

Although the reactions and the properties of the products in this series in general approximated to those recorded for analogous compounds containing the nitro- or amino-group in the 4′-position, some interesting differences have been found.

Sodium hydrogen 3-(4′-*nitro*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* is readily prepared from 4′-nitro-2′-methoxybenzene-2-naphthol-1-diazosulphonate *via* sodium 1-(4′-nitro-2′-methoxybenzeneazo)-β-naphthaquinone-1-sulphonate. Boiling with dilute hydrochloric acid converts it into 1-*hydroxy*-3-(4′-*nitro*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (I).

The methoxyl group is more stable than the phthalazine ring under demethylating conditions and the corresponding hydroxy-compound could not be prepared from (I). With boiling hydriodic acid (*d* 1·7) compound (I) gave ammonium iodide, indicating disruption of the phthalazine ring, and, after treatment of the product with sodium hydrogen sulphite solution, only an unidentified acid was obtained. Attempted demethylation of (I) with hydrobromic and acetic acids at 180° gave an intractable resin, whilst attempted demethylation with fuming hydrochloric acid at 180° gave 4′-*nitro*-2′-*methoxy*-3-*phenylphthalaz*-1-*one* (II) and 2-(4′-*nitro*-2′-*methoxyphenylamino*)iso*indolinone*-3-*acetic acid* (IV).

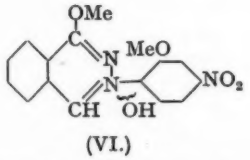


(IV) must be derived from (I) by opening of the phthalazine ring to benzo-4′-nitro-2′-methoxyphenylhydrazide-2-β-acrylic acid (III), followed by closure under the acid conditions employed to a 5-membered ring, this view being supported by the yellow colour of an alkaline solution of (IV), whereas analogues of (III) dissolve in alkalis with a bluish-violet colour (cf. Rowe *et al.*, *J.*, 1935, 1800; 1936, 1102), and by its ready conversion into the anhydro-compound, 2 : 5-*diketo*-3-(4′-*nitro*-2′-*methoxyphenyl*)iso*indolinopyrazolidocoline* (V), by means of acetic anhydride. Although long boiling with acetic anhydride and pyridine opens the phthalazine ring of 1-hydroxy-3-(2′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid with subsequent ring closure and elimination of water to form 2 : 5-diketo-3-(2′-nitrophenyl)*iso*-indolinopyrazolidocoline (*J.*, 1935, 1804), compound (I) under similar conditions is merely converted into its *O*-acetyl derivative.

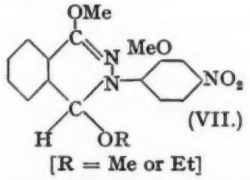
2-(4′-Nitro-2′-methoxyphenylamino)*iso*indolinone-3-acetic acid (IV) is the first example of a compound of this type with a nitro-group in the 4′-position, as hitherto analogues have only been obtained with the nitro-group in the 2′-position. When sodium 1-(2′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate is treated with sodium hydroxide and the mixture rapidly acidified, sodium benzaldehyde-2′-nitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid is obtained and is converted by boiling dilute hydrochloric acid into a mixture of benzo-2′-nitrophenylhydrazide-2-β-acrylic acid and 2-(2′-nitrophenylamino)*iso*indolinone-3-acetic acid (*J.*, 1935, 1800). Sodium 1-(4′-nitro-2′-methoxybenzeneazo)-β-naphthaquinone-1-sulphonate, treated similarly with sodium hydroxide and the mixture acidified after only 15 seconds, gave a product from which sodium benzaldehyde-2′-methoxy-4′-nitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid could not be isolated by fractional crystallisation, but, after boiling with dilute hydrochloric acid, a mixture (13·8%) of (I) and (IV) was obtained.

Heating 1-hydroxy-3-(2′-, 3′-, or 4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid with fuming hydrochloric acid at 180° also gave interesting results. The 4′-nitro-compound gave 4′-nitro-3-phenylphthalaz-1-one (14·9%) and 2-(4′-nitrophenylamino)*iso*indolinone-3-acetic acid (0·7%) (see Rowe, McFadyen, and Peters, following paper), whereas from the 3′-nitro-isomeride, only 3′-nitro-3-phenylphthalaz-1-one (45·9%) was formed and no trace of the corresponding *iso*indolinone derivative was detected. Contrary to anticipation, the 2′-nitro-isomeride gave resins, from which neither 2′-nitro-3-phenylphthalaz-1-one nor 2-(2′-nitrophenylamino)*iso*-indolinone-3-acetic acid could be isolated. On the other hand, 1-hydroxy-3-(4′-chloro-2′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid afforded a little (1%) 2-(4′-chloro-2′-nitrophenylamino)*iso*indolinone-3-acetic acid and a resin which appeared to consist essentially of 4′-chloro-2′-nitro-3-phenylphthalaz-1-one.

By refluxing (I) with aqueous sulphuric acid (b. p. 140°), not only is (II) formed, as would be expected, but also (IV) in about the same proportion as is obtained by heating (I) with fuming hydrochloric acid at 180°. With methyl sulphate, 4′-nitro-2′-methoxy-3-phenylphthalaz-1-one (II) gave a product which appears to be derived from (VI) by partial loss of water, resembling in this respect the analogous 2′ : 6′-dihalogeno-compounds (*J.*, 1931, 1076).



(VI.)



(VII.)

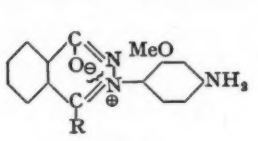
[R = Me or Et]

The methylated base crystallises from methyl or ethyl alcohol forming *compounds* (VII) which are combination products of the base and alcohol; when heated first at 100° and then at 140°, these merely lose the combined alcohol (cf. 2′ : 6′-dihalogeno-compounds, *loc. cit.*). This behaviour is unlike that of the analogous substances derived from 4′- or 3′-nitro-3-phenylphthalaz-1-one (Rowe, Himmat, and Levin, *J.*, 1928, 2554, 2562), for these are converted into 4-keto-1-methoxy-3-(4′- or 3′-nitrophenyl)-3 : 4-dihydrophthalazine by heating in this manner. Examination of the latter conversion has now shown that it is an oxidation process, for when methylated 4′-nitro-3-phenylphthalaz-1-one, crystallised from methyl alcohol, is heated in an atmosphere of carbon dioxide the transformation does not occur, whereas when heated in a measured volume of air the conversion proceeds readily with the absorption of 4 atoms of oxygen per molecule of methylated base.

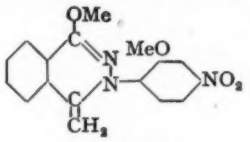
4′-*Nitro*-2′-*methoxy*-3-*phenyl*-4-*methylphthalaz*-1-*one*, prepared by the action of cold acid dichromate on (I) is converted by methyl sulphate and subsequent basification into

4′-nitro-1 : 2′-dimethoxy-3-phenyl-4-methylene-3 : 4-dihydrophthalazine (IX) which has similar properties to those of the analogues previously described (Rowe and Twitchett, *J.*, 1936, 1704). It condenses with chloro-2 : 4-dinitrobenzene forming *4′-nitro-1 : 2′-dimethoxy-3-phenyl-4-(2″ : 4″-dinitrobenzylidene)-3 : 4-dihydrophthalazine* (X). An attempt to confirm this type of constitution by refluxing 1-methoxy-3-(4′-nitrophenyl)-4-(2″ : 4″-dinitrobenzylidene)-3 : 4-dihydrophthalazine with aqueous sulphuric acid (1 : 1) for some hours failed; no 2 : 4-dinitrobenzaldehyde was formed because the sulphate is too stable for hydrolysis to occur.

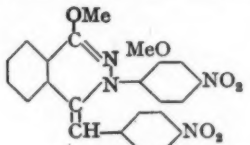
When heated with dilute hydrochloric acid at 180° (cf. Rowe *et al.*, J., 1937, 98), 4′-nitro-2′-methoxy-3-phenylphthalaz-1-one and its 4-methyl derivative are converted into *4′-nitro-2′-methoxy-3-phenylphthalaz-4-one* and its 1-*methyl* derivative, respectively; the constitutions of



(VIII.)



(IX.)



(X.)

the transformation products were confirmed synthetically by condensing *p*-nitro-*o*-methoxyphenylhydrazine with *o*-phthalaldehydic acid and acetophenone-*o*-carboxylic acid, respectively.

Reduction of 4′-nitro-2′-methoxy-3-phenylphthalaz-1-one and its 4-methyl derivative with sodium sulphide gives substances which are essentially *4′-amino-2′-methoxy-3-phenylphthalaz-1-one* and its 4-*methyl* derivative (VIII; R = H or Me), respectively, although analyses indicate that they are derived from (VIII) by combination with 1 mol. of water, tenaciously retained. The *acetyl* compounds, however, crystallise from water without combining with it. 4′-Amino-2′-methoxy-3-phenyl-4-methylphthalaz-1-one is unaffected by treatment with alkaline hydrosulphite, and in this respect is unlike 4′-amino-3-phenyl-2′-methylphthalaz-1-one and its 4-methyl derivative which are converted by this means into 1-keto-3-(4′-amino-2′-methylphenyl)tetrahydrophthalazine and its 4-methyl derivative, respectively (Rowe and Siddle, *J.*, 1932, 478). Reduction with zinc and hydrochloric acid, however, readily gives *4′-amino-2′-methoxy-N-phenyl-3-methylphthalimidine*, and *4′-amino-2′-methoxy-N-phenylphthalimidine* is similarly prepared from (II) or (VIII; R = H).

1-Hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid behaves in an exceptional manner when boiled with mineral acid. The anticipated 4′-amino-2′-methoxy-3-phenylphthalaz-1-one (VIII; R = H) is formed, but the main product of the reaction is its 4-methyl derivative (VIII; R = Me), decarboxylation occurring preferentially to the elimination of acetic acid. Similar behaviour has hitherto been observed only with 1-hydroxy-3-(benzeneazobenzene)-3 : 4-dihydrophthalazine-4-acetic acid (Rowe and Tomlinson, *J.*, 1932, 1120). When hydrochloric acid is used in this reaction, the initial formation of a sparingly soluble hydrochloride of 1-hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid favours the production of the 4-methyl derivative, whereas when the amino-acid is added to boiling hydrochloric acid so that a solution is immediately formed, the proportion of 4′-amino-2′-methoxy-3-phenylphthalaz-1-one in the product is considerably increased at the expense of its 4-methyl derivative. Similar behaviour was observed in the production of 4′-amino-2′-methoxy-*N*-phenylphthalimidine and its 3-methyl derivative from 1-hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid with tin and hydrochloric acid.

Experimental.

Sodium Hydrogen 3-(4′-Nitro-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate.—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (50 g.) in water (160 c.c.) was stirred slowly at 0° into a solution of diazotised 5-nitro-*o*-anisidine prepared by adding 2N-sodium nitrite solution (52 c.c.) to a suspension of the base (16·8 g.) in dilute hydrochloric acid (1 : 2, 180 c.c.) at 0—5°. 4′-Nitro-2′-methoxybenzene-2-naphthol-1-diazosulphonate separated as an orange precipitate. It was filtered off, washed free from acid, mixed with cold water (300 c.c.), and dissolved by adding a cold solution of anhydrous sodium carbonate (30 g.) in water (120 c.c.). The orange solution was added immediately to a cold solution of sodium hydroxide (25 g.) in water (50 c.c.); the temperature rose about 6° and the deep violet liquid after being kept overnight, had become yellowish-brown. The product was isolated in the usual manner after separation from 4′-nitro-2′-methoxybenzeneazo-β-naphthol (1·54 g.; 4·8%). The sodium hydrogen *salt* (34·4 g.; 73·2%) crystallised from water in amber-coloured, irregular prisms, containing $3H_2O$, m. p. 111—114° with evolution of water and partial re-solidification (Found: S, 6·3. $C_{17}H_{14}O_8N_2SNa,3H_2O$ requires S, 6·45%). Water of crystallisation was not completely removed at 200°; the anhydrous *compound* crystallised from absolute alcohol in deep yellow, small prisms, m. p. 283—284° (decomp.) after darkening at 265° (Found: S, 7·0.

$C_{17}H_{14}O_8N_3SNa$ requires S, 7·2%). It is a yellow acid dye of greater tinctorial power than the analogue from *p*-nitroaniline, but also fugitive to light.

1-*Hydroxy*-3-(4′-*nitro*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (I).—A solution of sodium hydrogen 3-(4′-nitro-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate (50 g.) in water (400 c.c.) was boiled and concentrated hydrochloric acid (250 c.c.) added gradually until the evolution of sulphur dioxide had ceased and the product was crystalline (about 12 hours). It was washed with boiling water and crystallised from ethyl acetate. The *acid* (I) formed pale yellow prisms, m. p. 231—233° (decomp.) (35·8 g.; 88·8%) (Found: C, 57·1; H, 4·4; N, 11·7; OMe, 8·5. $C_{17}H_{15}O_6N_3$ requires C, 57·1; H, 4·2; N, 11·8; OMe, 8·7%). It dissolved in sodium carbonate and hydroxide with orange and deep red colours, respectively, and in cold concentrated sulphuric acid with an orange colour, being reprecipitated unaltered on dilution.

Derivatives of (I).—The *methyl* ester crystallised from methyl alcohol in pale yellow prisms, m. p. 184—185° (Found: C, 58·1; H, 4·6; N, 11·5. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·6; N, 11·3%). The *ethyl* ester crystallised from alcohol in pale yellow, minute prisms, m. p. 155—156° (Found: C, 59·1; H, 5·2; N, 10·9. $C_{19}H_{19}O_6N_3$ requires C, 59·2; H, 4·9; N, 10·9%). Both esters were insoluble in sodium carbonate solution, but dissolved in aqueous sodium hydroxide with an orange colour. The O-*acetyl* derivative crystallised from ethyl acetate in pale yellow prisms, m. p. 186—187° (Found: C, 57·25; H, 4·3; N, 10·6. $C_{19}H_{17}O_7N_3$ requires C, 57·1; H, 4·3; N, 10·5%), soluble in cold sodium carbonate with a deep yellow colour and in sodium hydroxide with a deep red colour, hydrolysis of the acetyl group occurring in the latter case. The *N*-methyl ether, 1-*keto*-3-(4′-*nitro*-2′-*methoxyphenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid* (cf. Rowe and Peters, *J.*, 1933, 1069), crystallised from acetic acid in pale yellow prisms, m. p. 222—223° (Found: C, 58·3; H, 4·8; N, 11·6; OMe, 8·1. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·85; N, 11·3; OMe, 8·35%), soluble in cold dilute alkali solutions with a yellow colour. Its *methyl* ester crystallised from methyl alcohol in pale yellow plates, m. p. 152—153° (Found: C, 59·2; H, 5·0. $C_{19}H_{19}O_6N_3$ requires C, 59·2; H, 4·9%), insoluble in cold alkalis and hydrolysed by boiling aqueous sodium hydroxide.

1 : 4-*Diketo*-3-(4′-*nitro*-2′-*methoxyphenyl*)*tetrahydrophthalazine* (cf. Rowe, Gillan, and Peters, *J.*, 1935, 1811).—Powdered potassium permanganate (5 g.) was added gradually during 10 minutes to a fine suspension of (I) (5 g.) in water (50 c.c.) at 70°; the reaction was vigorous. The mixture was boiled, filtered, and acidified with hydrochloric acid after removal of some resinous matter from the cooled filtrate. The yellow, resinous precipitate was crystallised from dilute acetic acid (1 : 1) (0·25 g.; 5·7%) and then from alcohol (charcoal); the *compound* formed colourless needles, m. p. 256—257° (Found: C, 57·7; H, 3·8; N, 13·6; OMe, 9·8. $C_{15}H_{11}O_5N_3$ requires C, 57·5; H, 3·5; N, 13·4; OMe, 9·9%), soluble in aqueous alkalis with a yellow colour.

1-*Hydroxy*-3-(4′-*amino*-2′-*methoxyphenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid*.—Prepared from (I) (20 g.) by reduction with alkaline sodium hydrosulphite and precipitation with acid (13·3 g.; 72·6%), or less conveniently by heating a fine suspension of (I) (5 g.) in acid stannous chloride (20 g. in 50 c.c. of concentrated hydrochloric acid) on the steam-bath until dissolved (10 minutes) and isolating the amino-acid by rendering the solution alkaline with sodium carbonate, filtering, and precipitating from the filtrate by acidification (3·7 g.; 81·9%), the *acid* crystallised from a large volume of boiling water, or by adding hydrochloric acid to a hot solution in aqueous sodium carbonate, in colourless prisms, m. p. 203—204° (decomp.) (Found: C, 62·3; H, 5·2; N, 12·8; OMe, 9·3. $C_{17}H_{17}O_4N_3$ requires C, 62·4; H, 5·2; N, 12·8; OMe, 9·5%).

Action of Hydriodic Acid on (I).—A suspension of (I) (4 g.) in hydriodic acid (*d* 1·7; 20 c.c.) was heated in an oil-bath at 125—135° for 2½ hours; dissolution gradually proceeded and the volume was halved by evaporation. The solution was poured into a cold solution of sodium hydrogen sulphite (10 g.) in water (50 c.c.), stirred until the dark brown precipitate had dissolved, and treated with concentrated aqueous sodium carbonate until neutral to Congo-red. Next day, the yellow precipitate was collected; the filtrate, made alkaline with sodium hydroxide and boiled, gave much ammonia, indicating disruption of the phthalazine ring. The product (2·05 g.) crystallised from water (charcoal) in small, colourless needles which melted at 175—177°, then partially solidified, and by further heating slowly decomposed evolving gas (Found: C, 48·65; H, 5·15; N, 6·85; S, 4·1%), but this acid was not identified.

Action of Fuming Hydrochloric Acid and Aqueous Sulphuric Acid on (I).—The compound (4 g.) was heated with fuming hydrochloric acid (6 c.c.) in a sealed tube to 180° in ½ hour and kept at 180° for ½ hour. The mixture was made alkaline with aqueous sodium carbonate and kept for some hours with occasional stirring, the precipitate (for filtrate, see below) was then digested with boiling dilute sulphuric acid (1 : 5; 100 c.c.), and the solution was filtered from some tar, boiled (charcoal), and filtered. The crystals which separated on standing were basified by digestion with warm sodium carbonate solution; 4′-*nitro*-2′-*methoxy*-3-*phenylphthalaz*-1-*one* (II) (0·6 g.; 18·0%), crystallised first from alcohol and then from benzene–pyridine in pale yellow, hair-like needles, m. p. 228—229° (Found: C, 60·5; H, 4·0; N, 14·2; OMe, 10·2. $C_{15}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1; OMe, 10·4%), readily soluble in dyridine or alcohol, but almost insoluble in benzene. The alcoholic solution deposited pale yellow, hair-like needles, m. p. 207—209°, containing 1 mol. of solvent of crystallisation which was removed by heating at 130—140° for 2 hours (Found: loss, 12·5. $C_{15}H_{11}O_4N_3,C_2H_5OH$ requires loss, 13·4%). It was insoluble in aqueous sodium carbonate, but dissolved in sodium hydroxide solution with an orange colour. With mineral acids, salts were formed, the sulphate and hydrochloride crystallising in colourless needles; the *picrate* crystallised from alcohol in pale yellow needles, m. p. 229—231° (Found: C, 48·0; H, 2·8; N, 16·0. $C_{21}H_{14}O_{11}N_6$ requires C, 47·9; H, 2·7; N, 16·0%).

The filtrate mentioned above was rendered faintly acid with hydrochloric acid, and the precipitate collected, dried, and extracted with boiling ethyl acetate (charcoal); the concentrated filtrate gave 2-(4′-*nitro*-2′-*methoxyphenylamino*)*isoindolinone*-3-*acetic acid* (IV) (0·24 g.; 6·0%) which crystallised from ethyl acetate (charcoal) in very pale yellow needles, m. p. 231—232° (Found: C, 57·0; H, 4·2; N, 11·8; OMe, 8·8. $C_{17}H_{15}O_6N_3$ requires C, 57·1; H, 4·2; N, 11·8; OMe, 8·7%), slightly soluble in aqueous sodium hydrogen carbonate with a pale yellow colour and evolution of carbon dioxide. It dissolved in

aqueous sodium carbonate with an orange colour which became orange-red on addition of sodium hydroxide, and was precipitated unaltered by adding hydrochloric acid to the solution. The *methyl* ester crystallised from methyl alcohol in pale yellow needles, m. p. 144—146° (Found: C, 58·0; H, 4·4; N, 11·4. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·6; N, 11·3%). When (IV) (1 g.) was boiled with acetic anhydride (4 c.c.) for ½ hour, or with addition of pyridine (0·25 c.c.) for a few minutes, it was converted into 2 : 5-*diketo*-3-(4′-*nitro*-2′-*methoxyphenyl*)*iso*-*indolinopyrazolidocoline* (V) (0·85 g.; 89·5%) which crystallised from acetic acid in almost colourless prisms, m. p. 227—228° (Found: C, 60·1; H, 3·85; N, 12·4. $C_{17}H_{13}O_5N_3$ requires C, 60·2; H, 3·8; N, 12·4%), insoluble in cold alkalis, but slowly soluble in boiling aqueous sodium hydroxide, with an orange-red colour. Compound (V) was best hydrolysed to (IV) by boiling an acetic acid solution with hydrochloric acid for ½ hour.

A mixture of (IV) and (II) was also obtained by refluxing a fine suspension of (I) (20 g.) in water (120 c.c.) and concentrated sulphuric acid (100 c.c.) for 1½ hours. The greenish-black product was diluted with water (400 c.c.), boiled, and filtered hot; the black residue (for filtrate, see below), after being washed with hot water, was dissolved in cold aqueous 10% sodium carbonate, the solution filtered, and the filtrate acidified with hydrochloric acid. The dried precipitate was dissolved in boiling ethyl acetate and the solution filtered; the concentrated filtrate deposited pale yellow needles of (IV), m. p. 231—232° (0·6 g.; 3·0%). The filtrate mentioned above, after standing over-night, deposited hair-like needles, which were digested with warm dilute sodium carbonate solution, filtered off (for filtrate, see below), and crystallised first from alcohol and then from benzene–pyridine to form pale yellow, hair-like needles of (II), m. p. 228—229° (3·6 g.; 21·6%). The sodium carbonate extract mentioned above was acidified with hydrochloric acid; the dried precipitate crystallised from ethyl acetate in pale yellow needles of (IV), m. p. 231—232° (0·6 g.; 3·0%).

Compound (IV) was prepared in quantity as follows. A cold solution of sodium hydroxide (125 g.) in water (250 c.c.) was rapidly stirred into a solution of sodium 1-(4′-nitro-2′-methoxybenzeneazo)-β-naphthaquinone-1-sulphonate prepared from 5-nitro-*o*-anisidine (84 g.) as already described (cf. p. 463). After 15 seconds, the mixture was acidified by adding hydrochloric acid (715 c.c.) together with ethyl acetate (300 c.c.) to control frothing. The mixture was then made alkaline with sodium carbonate, 4′-nitro-2′-methoxybenzeneazo-β-naphthol (25·2 g.; 15·6%) filtered off, and the filtrate rendered faintly acid to Congo-red with hydrochloric acid and saturated with sodium chloride. A mixture of sodium benzaldehyde 4′-nitro-2′-methoxyphenylhydrazone-ω-sulphonate-2-β-acrylate and sodium hydrogen 3-(4′-nitro-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate was obtained. Attempts to separate this mixture by fractional precipitation of a solution in aqueous sodium carbonate by means of hydrochloric acid were unsuccessful. The mixture was hydrolysed by boiling with dilute hydrochloric acid until the evolution of sulphur dioxide had ceased, and the product crystallised from ethyl acetate (charcoal). The pale yellow crystals (70 g.), together with a further amount obtained by concentrating the filtrate, were boiled with 4 times their weight of acetic anhydride for 15 minutes; the solution, after being kept over-night, deposited almost colourless prisms of 2 : 5-diketo-3-(4′-nitro-2′-methoxyphenyl)*iso*indolinopyrazolidocoline (V), m. p. 227—228° (23·35 g.; 13·8%), hydrolysed to (IV) as described above.

Action of Methyl Sulphate on 4′-Nitro-2′-methoxy-3-phenylphthalaz-1-one (II).—Methyl sulphate (0·5 g.) was added to a solution of (II) (1 g.) in dry nitrobenzene (4 c.c.); after ½ hour at 120°, the nitrobenzene was removed with steam, and the cooled aqueous residue filtered and basified with aqueous sodium carbonate. The washed and dried precipitate (1·0 g.) crystallised from ethyl acetate in small yellow prisms which reddened progressively above 160°, softened at about 205°, and melted at 261—264°. The analytical results for this specimen did not agree with formula (VI), but suggest that the substance is derived from it by partial loss of water (cf. analogous compounds, Rowe, Dunbar, and Williams, *J.*, 1931, 1076) (Found: C, 60·15; H, 4·5; N, 13·5; OMe, 17·4). When the base (1 g.) was heated with acetic acid (1 c.c.) and hydrobromic acid (2 c.c.) at 150° for ½ hour, most of it was recovered unchanged; the remainder was converted by partial demethylation into (II) (0·15 g.; 16·6%).

The methylated base was insoluble in cold aqueous alkalis, but dissolved readily in cold concentrated hydrochloric acid with a pale yellow colour. Addition of 20% perchloric acid (10 c.c.) to a solution of the base (1 g.) in concentrated hydrochloric acid (3 c.c.), and cooling in a freezing mixture for ½ hour, gave a crystalline precipitate of 4′-*nitro*-1 : 2′-*dimethoxy*-3-*phenylphthalazinium perchlorate* (1·24 g.; 93·9%) which crystallised from 50% acetic acid containing a little perchloric acid in colourless, lustrous leaflets with a faint yellow tinge, m. p. 209—211°; these explode when strongly heated (Found: C, 46·4; H, 3·35; N, 10·2; Cl, 8·5. $C_{16}H_{14}O_8N_3Cl$ requires C, 46·7; H, 3·4; N, 10·2; Cl, 8·6%).

The methylated base dissolved readily in methyl or ethyl alcohol, and the solutions deposited crystals which consisted of the combination products of the base with 1 mol. of alcohol (VII). The base crystallised from methyl alcohol in yellow prisms, m. p. 161—163° [Found: C, 59·7; H, 5·1; N, 12·0; OMe, 25·2; (freshly prepared material), 26·6. $C_{17}H_{17}O_5N_3$ requires C, 59·5; H, 5·0; N, 12·2; OMe, 27·1%], and from ethyl alcohol in yellow prismatic needles, m. p. 116—117° [Found: C, 60·9; H, 5·5; N, 11·8; OR (calc. as OMe), 25·3. $C_{18}H_{19}O_5N_3$ requires C, 60·5; H, 5·3; N, 11·8; OR (calc. as OMe), 26·05%].

4′-*Nitro*-2′-*methoxy*-3-*phenylphthalaz*-4-*one*.—(1) Following the method of Davies (*J.*, 1922, **121**, 715), 5-nitro-*o*-anisidine was converted into p-*nitro*-o-*methoxyphenylhydrazine*, orange needles (from alcohol), m. p. 152—153° (Found: C, 45·8; H, 5·0; N, 22·9. $C_7H_9O_3N_3$ requires C, 45·9; H, 4·9; N, 22·9%). A hot solution of the latter (1·83 g.) in alcohol (60 c.c.) was added to a hot solution of *o*-phthalaldehydic acid (1·5 g.) in water (40 c.c.) and the mixture refluxed (cf. Rowe and Levin, *J.*, 1928, 2555). The *lactone* form of o-*carboxybenzaldehyde* p-*nitro*-o-*methoxyphenylhydrazone* crystallised in orange prismatic needles, m. p. 223—224° (Found: C, 57·1; H, 4·0; N, 13·4. $C_{15}H_{13}O_5N_3$ requires C, 57·1; H, 4·1; N, 13·3%), soluble in aqueous sodium carbonate and sodium hydroxide with yellow and red colours, respectively. Water was eliminated by dissolving the compound in cold concentrated sulphuric acid and pouring on ice after ½ hour. 4′-*Nitro*-2′-*methoxy*-3-*phenylphthalaz*-4-*one* crystallised from alcohol in pale cream-coloured prisms, m. p. 175—176° (Found: C, 60·8; H, 3·7; N, 13·9; OMe, 10·0. $C_{16}H_{11}O_4N_3$ requires C, 60·6; H, 3·7; N, 14·1; OMe, 10·4%), insoluble in alkalis or hydrochloric acid.

(2) 4′-Nitro-2′-methoxy-3-phenylphthalaz-1-one (1 g.) was heated with aqueous hydrochloric acid (18 c.c.; 1 : 8) at 180° for 6 hours (cf. Rowe, Adams, Peters, and Gillam, *J.*, 1937, 98). After unaltered material (0·26 g.; 26%) had been extracted with boiling dilute hydrochloric acid, 4′-nitro-2′-methoxy-3-phenylphthalaz-4-one crystallised from alcohol in pale cream prisms, m. p. and mixed m. p. 175—176° (0·53 g.; 53%).

4′-Amino-2′-methoxy-3-phenylphthalaz-4-one.—Hot solutions of stannous chloride (4 g.) in hydrochloric acid (10 c.c.) and 4′-nitro-2′-methoxy-3-phenylphthalaz-4-one (1 g.) in acetic acid (5 c.c.) were mixed and brought to b. p.; after cooling, the colourless needles were collected and basified with aqueous sodium hydroxide. The *amino*-compound crystallised from alcohol in colourless plates, m. p. 215—216° (0·7 g.; 77·8%) (Found: C, 67·6; H, 4·8; N, 15·6; OMe, 11·9. $C_{15}H_{13}O_3N_3$ requires C, 67·4; H, 4·9; N, 15·7; OMe, 11·6%). It was also obtained (50·7%) by treating *o*-carboxybenzaldehyde *p*-nitro-*o*-methoxyphenylhydrazone similarly. The *acetyl* derivative crystallised from alcohol in colourless prisms, m. p. 232—233° (Found: C, 66·0; H, 5·0; N, 13·5. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·85; N, 13·6%).

4′-Amino-2′-methoxy-3-phenylphthalaz-1-one (VIII; R = H).—A solution of sodium sulphide crystals (32 g.) in water (32 c.c.) was added to a boiling suspension of (II) (4 g.) in water (400 c.c.); the resulting deep red solution became orange after boiling for 10 minutes and, when cool, deposited long, golden-yellow needles, m. p. 225—226° (decomp.) (2·0 g.). The substance crystallised from absolute alcohol (charcoal) in yellow prisms, m. p. 260—261° (decomp.) after softening and darkening at 240° (Found: C, 64·6; H, 5·2; N, 15·1; OMe, 11·6%). Since the analytical result for carbon was not what was anticipated, the base was purified by conversion into its acetyl derivative which was subsequently hydrolysed.

4′-Acetamido-2′-methoxy-3-phenylphthalaz-1-one crystallised from water in fine, colourless needles m. p. 285—286° (Found: C, 65·9; H, 5·0; N, 13·6. $C_{17}H_{15}O_3N_3$ requires C, 66·0; H, 4·85; N, 13·6%), which became yellow on exposure to light and air. The acetyl compound (1 g.) was hydrolysed by boiling with concentrated hydrochloric acid (20 c.c.) for 10 minutes and basifying the colourless needles of the hydrochloride by digesting with dilute sodium carbonate solution. *4′-Amino-2′-methoxy-3-phenylphthalaz-1-one* crystallised from absolute alcohol in pale yellow prisms, m. p. 267—268° (decomp.) after softening at 261° (Found: C, 64·8; H, 4·9; N, 15·1. $C_{15}H_{13}O_2N_3$ requires C, 67·4; H, 4·9; N, 15·7%). Thus, in spite of the higher m. p. of this specimen of the base, the analytical result for carbon remained unsatisfactory.

4′-Amino-2′-methoxy-N-phenylphthalimidine.—(*a*) This was most conveniently prepared by adding zinc dust (3 g.) in small portions during ½ hour to a vigorously boiling solution of (II) (2 g.) in hydrochloric acid (40 c.c.) and water (100 c.c.). The cooled solution was made alkaline with sodium hydroxide, the dried precipitate extracted with boiling alcohol, and the extract concentrated. The *phthalimidine* (1·05 g.; 61·4%) crystallised from alcohol (charcoal) in colourless, lustrous, rectangular plates, m. p. 237° (Found: C, 70·6; H, 5·6; N, 11·0; OMe, 12·75. $C_{15}H_{14}O_3N_2$ requires C, 70·9; H, 5·5; N, 11·0; OMe, 12·2%). The *acetyl* derivative crystallised from dilute acetic acid in colourless needles, m. p. 247—248° (Found: C, 68·8; H, 5·5; N, 9·7. $C_{17}H_{16}O_3N_2$ requires C, 68·9; H, 5·4; N, 9·5%).

(*b*) The phthalimidine was obtained by reducing 4′-amino-2′-methoxy-3-phenylphthalaz-1-one (1 g.) in hydrochloric acid (20 c.c.) and water (50 c.c.) with zinc dust (1 g.).

(*c*) Powdered 1-hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid (10 g.) was added in portions to boiling concentrated hydrochloric acid (200 c.c.) and the solution refluxed for 14 hours with gradual addition of granulated tin (20g.). The phthalimidine (0·85 g.; 10·9%) was isolated by rendering the product alkaline with aqueous sodium hydroxide and extracting the dried precipitate with alcohol. When, in a similar experiment, 1-hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid was ground with the concentrated hydrochloric acid and the suspension of the difficultly soluble hydrochloride boiled (much frothing) until dissolved (¼ hour) and then reduced, a mixture of the phthalimidine (0·37 g.; 4·8%) and its 3-methyl derivative (0·4 g.; 4·9%) was obtained, separation being effected by fractional crystallisation from alcohol.

(*d*) A suspension of 1-hydroxy-3-(4′-nitro-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid (20 g.) in stannous chloride (80 g.) and hydrochloric acid (200 c.c.) was warmed on the steam-bath until dissolved (15 minutes); hydrochloric acid (300 c.c.) was added and the solution refluxed for 14 hours with gradual addition of granulated tin (40 g.). The cooled solution was made alkaline with aqueous sodium hydroxide and the dried precipitate extracted with boiling alcohol (150 c.c.); the extract, on keeping, deposited crystals of the phthalimidine (0·7 g.; 4·9%). The filtrate, on concentration, gave a mixture (0·95 g.) of colourless leaflets of 4′-amino-2′-methoxy-*N*-phenylphthalimidine and yellow prisms of 4′-amino-2′-methoxy-3-phenylphthalaz-1-one, identified by mechanical separation and mixed m. p. determinations.

4′-Nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one.—A solution of (I) (40 g.) in cold concentrated sulphuric acid (400 c.c.) was poured on ice (1200 g.) and stirred mechanically, and powdered potassium dichromate (18 g.) was added gradually during ¾ hour. After 3 hours' stirring, the crystalline precipitate was collected and digested with warm water for several hours, during which decomposition slowly occurred with evolution of carbon dioxide. The mixture was rendered faintly alkaline with aqueous sodium carbonate, and the precipitate collected and crystallised from boiling dilute hydrochloric acid (charcoal). 4′-Nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one hydrochloride (22·5 g.; 57·8%) was basified by grinding with dilute sodium carbonate solution. *4′-Nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one* crystallised from benzene–pyridine (2 : 1) (charcoal) in pale yellow prisms, m. p. 223—224° (decomp.) (Found: C, 61·8; H, 4·3; N, 13·5; OMe, 9·8. $C_{16}H_{13}O_4N_3$ requires C, 61·7; H, 4·2; N, 13·5; OMe, 10·0%), readily soluble in pyridine or alcohol, almost insoluble in benzene. It was insoluble in aqueous sodium carbonate, but dissolved in aqueous sodium hydroxide with an orange colour; the hydrochloride and sulphate crystallised in small colourless prisms. The *picrate* formed yellow prisms (from alcohol), m. p. 216—217° (decomp.) (Found: C, 48·95; H, 3·2; N, 15·5. $C_{22}H_{16}O_{11}N_6$ requires C, 48·9; H, 3·0; N, 15·55%).

Action of Methyl Sulphate on 4′-Nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one.—A solution of 4′-nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one (10 g.) in hot dry nitrobenzene (40 c.c.) was

treated with methyl sulphate (4 c.c.) as already described for (II). Crystallisation of the orange-red base from ethyl acetate gave *4'-nitro*-1 : 2'-*dimethoxy*-3-*phenyl*-4-*methylene*-3 : 4-*dihydrophthalazine* (IX), dark red, almost black prisms with a green reflex, m. p. 146—147° (8·8 g.; 84·2%) (Found : C, 62·9; H, 4·6; N, 13·1; OMe, 18·6. $C_{17}H_{15}O_4N_3$ requires C, 62·8; H, 4·6; N, 12·9; OMe, 19·1%), insoluble in alkalis, but soluble in acids. When the base was heated with acetic acid and hydrobromic acid at 150° for ½ hour, it was not re-converted into 4'-nitro-2'-methoxy-3-phenyl-4-methylphthalaz-1-one (cf. Rowe, Levin, and Peters, *J.*, 1931, 1071), unaltered material only being recovered. Longer heating (1 hour) gave an unidentified substance, soluble in aqueous sodium carbonate with a yellow colour.

4'-Nitro-1 : 2'-*dimethoxy*-3-*phenyl*-4-*methylphthalazinium perchlorate*, prepared in a similar manner to 4'-nitro-1 : 2'-dimethoxy-3-phenylphthalazinium perchlorate, crystallised from 50% acetic acid containing perchloric acid in colourless prisms with a yellow tinge, m. p. 199—200° (74·4%); when heated strongly, the salt melts and explodes (Found : C, 47·5; H, 3·8; N, 10·0; Cl, 8·5. $C_{17}H_{16}O_8N_3Cl$ requires C, 47·9; H, 3·8; N, 9·9; Cl, 8·3%).

4'-Nitro-1 : 2'-*dimethoxy*-3-*phenyl*-4-(2'' : 4''-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine* (X).—This *compound*, prepared from 4'-nitro-1 : 2'-dimethoxy-3-phenyl-4-methylene-3 : 4-dihydrophthalazine (2 g.) as described by Rowe and Twitchett (*J.*, 1936, 1712) for the 4'-nitro-analogue, crystallised from acetic anhydride in deep orange-red, almost black prisms with a green reflex, m. p. 226—227° (2·42 g.; 80·1%) (Found : C, 56·5; H, 3·5; N, 14·2; OMe, 12·6. $C_{23}H_{17}O_8N_5$ requires C, 56·2; H, 3·5; N, 14·3; OMe, 12·6%).

4'-Nitro-2'-methoxy-3-*phenyl*-1-*methylphthalaz*-4-*one*.—(*a*) A solution of *p*-nitro-*o*-methoxyphenylhydrazine in alcohol was added to an aqueous solution of an equimolecular proportion of acetophenone-*o*-carboxylic acid at about 70° (cf. Rowe, Heath, and Patel, *J.*, 1936, 313); *o-carboxyacetophenone p-nitro-o-methoxyphenylhydrazone* (or its *lactone* form) crystallised in glistening yellow leaves (94·2%) (Found : C, 58·2; H, 4·5; N, 12·8. $C_{16}H_{15}O_5N_3$ requires C, 58·4; H, 4·6; N, 12·8%), soluble in aqueous sodium carbonate and sodium hydroxide with yellow and orange colours, respectively. When heated, it became pale yellow at about 180° owing to formation of *4'-nitro-2'-methoxy*-3-*phenyl*-1-*methylphthalaz*-4-*one*, and then melted at 237—238°, but this conversion was more conveniently effected by dissolving in cold concentrated sulphuric acid and pouring on ice next day; the product crystallised from alcohol in colourless, rhomboidal plates, m. p. 237—238° (Found : C, 61·8; H, 4·15; N, 13·7; OMe, 10·4. $C_{16}H_{13}O_4N_3$ requires C, 61·7; H, 4·2; N, 13·5; OMe, 10·0%), insoluble in sodium hydroxide or hydrochloric acid.

(*b*) The hydrochloride of 4'-nitro-2'-methoxy-3-phenyl-4-methylphthalaz-1-one (1·5 g.) was heated with hydrochloric acid (1·5 c.c.) and water (16·5 c.c.) at 180° for 6 hours (cf. Rowe, Adams, Peters, and Gillam, *loc. cit.*); the product, after purification by extraction with boiling dilute hydrochloric acid, was 4'-nitro-2'-methoxy-3-phenyl-1-methylphthalaz-4-one (0·74 g.; 55%).

4'-Amino-2'-methoxy-3-*phenyl*-1-*methylphthalaz*-4-*one*.—This *compound* was prepared similarly to 4'-amino-2'-methoxy-3-phenylphthalaz-4-one, except that acetic acid (10 c.c.) was used, and crystallised from alcohol in small, colourless plates or prisms, m. p. 258—259° (86·4%) (Found : C, 68·1; H, 5·4; N, 15·3; OMe, 11·4. $C_{16}H_{15}O_2N_3$ requires C, 68·3; H, 5·3; N, 14·95; OMe, 11·0%). It was also prepared (84·3%) by treating *o*-carboxyacetophenone-*p*-nitro-*o*-methoxyphenylhydrazone similarly. The *acetyl* derivative crystallised from dilute acetic acid in colourless needles, from acetic anhydride in small colourless prisms, and from alcohol in prismatic needles which, after being heated at 120° for 2 hours and cooled, spontaneously fracture into fine curved needles; all forms melt at 237—238° (Found in material crystallised from dilute acetic acid : C, 65·0; H, 5·3; N, 12·6. Found in material from alcohol : C, 64·6; H, 5·4; N, 12·65. Found in material heated at 120° for 2 hours : C, 64·2; H, 5·25. $C_{18}H_{17}O_3N_3$ requires C, 66·9; H, 5·3; N, 13·0. $C_{18}H_{17}O_3N_3,\frac{1}{2}H_2O$ requires C, 65·1; H, 5·4; N, 12·65%). Similar observations are recorded by Rowe *et al.* (*J.*, 1935, 1801) in the case of the acetyl derivative of 2 : 5-diketo-3-(2'-aminophenyl)*iso*indolinopyrazolidocoline.

4'-Amino-2'-methoxy-3-*phenyl*-4-*methylphthalaz*-1-*one* (VIII; R = Me).—A solution of sodium sulphide crystals (8 g.) in water (8 c.c.) was added to a boiling solution of 4'-nitro-2'-methoxy-3-phenyl-4-methylphthalaz-1-one (1 g.) in water (100 c.c.); the deep purple-red solution became orange after boiling for a few minutes and crystals began to separate. The *amino*-compound (0·8 g.; 88·5%) crystallised from alcohol in pale yellow prisms, m. p. 287—288° (decomp.) after darkening at 260° (Found : C, 64·1; H, 5·6; N, 14·0; OMe, 10·1. $C_{16}H_{15}O_2N_3,H_2O$ requires C, 64·2; H, 5·7; N, 14·05; OMe, 10·4%). The *acetyl* derivative crystallised from water (charcoal) in colourless prisms, m. p. 296—297° (decomp.) (Found : C, 66·8; H, 5·5; N, 13·1. $C_{18}H_{17}O_3N_3$ requires C, 66·9; H, 5·3; N,13·0%), which became brown on exposure to light and air.

4'-Amino-2'-methoxy-3-phenyl-4-methylphthalaz-1-one could not be prepared from 1-hydroxy-3-(4'-amino-2'-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid by the action of cold acid dichromate (cf. Rowe, Levin, and Peters, *J.*, 1931, 1071). Treatment of a solution of the amino-acid in aqueous sodium carbonate with potassium permanganate (cf. Rowe, Dunbar, and Williams, *J.*, 1931, 1087) gave impure 4'-amino-2'-methoxy-3-phenyl-4-methylphthalaz-1-one (11·6%). More satisfactory results were obtained by the following methods :

(*a*) A solution of the amino-acid (40 g.) in concentrated sulphuric acid (200 c.c.) and water (240 c.c.) was refluxed for 2 hours. Considerable frothing occurred initially. The brown solution was diluted with water (800 c.c.), boiled (charcoal), filtered, cooled, and made alkaline with anhydrous sodium carbonate. Next day, the crystalline precipitate was repeatedly extracted with boiling water and the combined extracts were concentrated. The product (7·7 g.) crystallised from water (charcoal) in yellow prisms, m. p. 267—268° (decomp.), and was a mixture of 4'-amino-2'-methoxy-3-phenylphthalaz-1-one and its 4-methyl derivative in the proportion of about 1 : 12, as shown by acetylation and fractional crystallisation of the acetyl derivatives from water.

A similar mixture was produced by grinding the amino-acid (10 g.) with cold concentrated hydrochloric acid (250 c.c.), refluxing the suspension of the difficultly soluble hydrochloride until dissolved (½ hour; considerable frothing), and boiling for 16 hours. The deep brown filtered solution was almost neutralised with sodium hydroxide, cooled, filtered, and made alkaline with sodium carbonate. The greenish-yellow

precipitate (2·5 g.) crystallised from water (charcoal) in yellow prisms, m. p. 267—268° (decomp.), identical with the mixture described above. On the other hand, when the amino-acid (10 g.) was added in portions during 5 minutes to boiling concentrated hydrochloric acid (250 c.c.) it immediately dissolved almost completely. After 16 hours' refluxing and subsequent treatment of the product as described above, a mixture (3·45 g.) of 4′-amino-2′-methoxy-3-phenylphthalaz-1-one and its 4-methyl derivative in the proportion of about 1 : 5·5 was obtained.

(*b*) A solution of the amino-acid (4 g.) in water (40 c.c.) and sodium hydroxide (4 g.) was refluxed; crystals of 4′-amino-2′-methoxy-3-phenyl-4-methylphthalaz-1-one separated progressively and were removed at intervals (after 12 hours' boiling, 0·98 g.; 28·5%). No 4′-amino-2′-methoxy-3-phenylphthalaz-1-one was formed.

(*c*) A solution of the amino-acid (2 g.) in water (40 c.c.) and sodium hydroxide (4 g.) was treated at 50° for ½ hour with hydrogen peroxide (8 c.c. of 20 vol.), added in two portions; the pale yellow solution deepened in colour and was heated on the steam-bath for 15 minutes to give 4′-amino-2′-methoxy-3-phenyl-4-methylphthalaz-1-one (1·2 g.; 69·8%).

4′-Amino-2′-methoxy-N-phenyl-3-methylphthalimidine.—Zinc dust (20 g.) was gradually added during ½ hour to a vigorously boiling solution of the hydrochloride of 4′-nitro-2′-methoxy-3-phenyl-4-methylphthalaz-1-one (10 g.) in hydrochloric acid (200 c.c.) and water (200 c.c.). After the cooled solution had been made alkaline with aqueous sodium hydroxide, the pink precipitate was dried, extracted with alcohol (charcoal), filtered, and the filtrate concentrated. *4′-Amino-2′-methoxy-N-phenyl-3-methylphthalimidine* (5·1 g.; 66·1%) crystallised from alcohol in colourless prisms, m. p. 191—192° (Found: C, 71·7; H, 6·0; N, 10·6; OMe, 11·3. $C_{16}H_{16}O_2N_2$ requires C, 71·6; H, 6·0; N, 10·45; OMe, 11·6%). The *acetyl* derivative crystallised from ethyl acetate in colourless prisms, m. p. 209—210° (Found: C, 69·6; H, 5·9; N, 9·2. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%).

The amino-phthalimidine was also prepared (*a*) by reducing 4′-amino-2′-methoxy-3-phenyl-4-methylphthalaz-1-one as described in the case of the corresponding 4′-nitro-compound, and (*b*) together with an equal proportion of 4′-amino-2′-methoxy-*N*-phenylphthalimidine by boiling a suspension of the difficultly soluble hydrochloride of 1-hydroxy-3-(4′-amino-2′-methoxyphenyl)-3 : 4-dihydrophthalazine-4-acetic acid with tin and hydrochloric acid (cf. p. 466).

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93. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XX. The Stabilities of Acrylic Acid Derivatives from Sodium 1-Arylazo-β-naphthaquinone-1-sulphonate and its Derivatives, and an Investigation of derived* iso*Indolinones.*

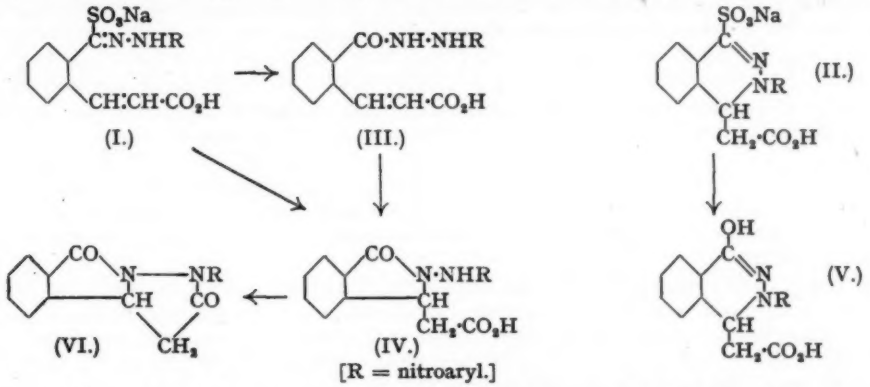
By (the late) F. M. ROWE, W. T. MCFADYEN, and A. T. PETERS.

Following the work of Rowe and Cross (preceding paper), it is shown that restricted action of sodium hydroxide on sodium 1-(4′-nitroarylazo)-β-naphthaquinone-1-sulphonate affords some sodium benzaldehyde 4′-nitroarylhydrazone-ω-sulphonate-2-β-acrylic acid (I). The amount of the latter formed is determined by hydrolysis to 2-(4′-*nitroarylamino*)iso*indolinone*-3-*acetic acid* (IV). The ease of opening of the sodium 1-(nitroarylazo)-β-naphthaquinone-1-sulphonates to give (I) is in the order R = 3′-nitro- > 4′-nitro- > 4′-nitro-2′-methyl > 2′-halogeno-4′-nitro- > 2′ : 6′-dibromo-4′-nitro- > 2′ : 6′-dichloro-4′-nitro-phenyl. Once formed, (I) is most stable when R = 2′ : 6′-dihalogeno-4′-nitrophenyl, and the stability decreases in the reverse order to that given above; finally where R = 3′-nitrophenyl, there is immediate formation of sodium hydrogen 3-(3′-nitrophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate [as (II)] and no trace of the isomeride.

IN Part XIII of this series (*J.*, 1935, 1796), it was shown that limited action of aqueous sodium hydroxide on sodium 1-(2′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate gave sodium benzaldehyde 2′-nitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid (I; R = 2′-nitrophenyl), whereas further action of sodium hydroxide gave sodium hydrogen 3-(2′-nitrophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate (II; R = 2′-nitrophenyl). Boiling dilute hydrochloric acid hydrolyses these sodium salts, (I) giving a mixture of benzo-2′-nitrophenylhydrazide-2-β-acrylic acid (III; R = 2-nitrophenyl) and 2-(2′-nitrophenylamino)*iso*indolinone-3-acetic acid (IV; R = 2′-nitrophenyl), whereas (II) gives 1-hydroxy-3-(2′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (V; R = 2′-nitrophenyl) (see p. 469).

Compounds of type (II) and (V) had been obtained previously where R = 4′- and 3′-nitrophenyl, 4′-nitro-2′-methylphenyl, and 2′-halogeno- and 2′ : 6′-dihalogeno-4′-nitrophenyl (*J.*, 1926, 699; 1928, 2558; 1931, 1078; 1932, 13, 476; 1935, 1135), but the existence of an intermediate compound of type (I) had only been postulated. The actual isolation of such a compound therefore was limited to derivatives from *o*-nitroaniline and its homologues (see also *J.*, 1936,

1098). An observation by Rowe and Cross (preceding paper), however, that it is possible to isolate 3-(4′-nitro-2′-methoxyphenylamino)*iso*indolinone-3-acetic acid (IV; R = 4′-nitro-2′-



[R = nitroaryl.]

methoxyphenyl) as one of the hydrolysis products of the mixture of sulphonic acids obtained by restricted action of aqueous sodium hydroxide on sodium 1-(4′-nitro-2′-methoxybenzeneazo)-β-naphthaquinone-1-sulphonate, led to an investigation of compounds (I), where R did not contain an *o*-nitro-substituent. It has now been found that compounds (I) are more stable than was anticipated. A point of interest is the influence of the substituents in the phenyl ring on the ease of opening of the β-naphthaquinone derivative and the stability of the resulting acrylic acid compound (I) to sodium hydroxide. Conditions of reaction in each case were kept as strictly comparable as possible.

Sodium 1-(4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate reacts with sodium hydroxide after several hours to give sodium hydrogen 3-(4′-nitrophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate (II; R = 4′-nitrophenyl), together with a little 4′-nitrobenzeneazo-β-naphthol (*loc. cit.*). When the action in sodium hydroxide was limited to 15 seconds, however, there was an increase in the yield of azo-β-naphthol derivative corresponding to the stability of the above β-naphthaquinone compound. The resultant mixture of sodium sulphonates was hydrolysed and examined. Comparable results were obtained whether or not the sodium salts were isolated before hydrolysis. Fractional crystallisation of the hydrolysis product from ethyl acetate showed that it was mainly (V; R = 4′-nitrophenyl), with some (IV; R = 4′-nitrophenyl). No derivative of type (III) was detected either in this case or in any other described in this paper.

2-(4′-*Nitrophenylamino*)iso*indolinone*-3-*acetic acid* (IV; R = 4′-nitrophenyl) was isolated most readily from the more soluble fractions by conversion into 2 : 5-*diketo*-3-(4′-*nitrophenyl*)iso-*indolinopyrazolidocoline* (VI; R = 4′-nitrophenyl) by refluxing with acetic anhydride and a little pyridine for 5 minutes, followed by hydrolysis with warm concentrated sulphuric acid, boiling aqueous-alcholic sodium hydroxide, or, preferably, boiling hydrochloric and acetic acids. The maximum yield of (IV; R = 4′-nitrophenyl) (13%) was obtained after interaction of sodium 1-(4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate and sodium hydroxide for 15 seconds.

Derivatives from 2-chloro-4-nitroaniline were studied in detail because the chlorine atom in the 2′-position increased the stability of (I; R = 2′-chloro-4′-nitrophenyl) to sodium hydroxide, and enabled it to be isolated without any (II; R = 2′-chloro-4′-nitrophenyl). When a mixture of sodium sulphonates was obtained, its composition was determined by hydrolysis to compounds (IV and V; R = 2′-chloro-4′-nitrophenyl) and separation of the latter. The maximum yield of (IV), *viz.* 61%, was obtained after interaction of the β-naphthaquinone compound in sodium hydroxide for 45 seconds. It was converted into 2 : 5-*diketo*-3-(2′-*chloro*-4′-*nitrophenyl*)iso-*indolinopyrazolidocoline* (VI; R = 2′-chloro-4′-nitrophenyl) similarly to the 4′-nitro-analogue. Compound (VI; R = 2′-chloro-4′-nitrophenyl) was reduced to the corresponding amino-compound by iron and aqueous acetic acid.

2-(2′-*Chloro*-4′-*aminophenylamino*)iso*indolinone*-3-*acetic acid* (IV; R = 2′-chloro-4′-amino-phenyl) was obtained by reducing the nitro-compound (IV) in various ways and was also prepared from (VI; R = 2′-chloro-4′-aminophenyl) by the rapid action of aqueous-alcoholic potassium hydroxide at 80°. It was reconverted into the anhydro-derivative (VI; R = 2′-chloro-4′-aminophenyl) by refluxing with phosphorus trichloride and toluene, but was

unchanged by refluxing with concentrated hydrochloric acid or aqueous sulphuric acid, or by heating with concentrated hydrochloric acid at 200°.

Sodium 1-(2′ : 6′-dichloro-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate was relatively very stable to aqueous sodium hydroxide, being unchanged after 15 seconds reaction, and, even after 2 hours, only about half of it was attacked. It is the most stable of the analogues examined. The chlorine atoms in the 2′ : 6′-positions also resulted in increased stability of (I; R = 2′ : 6′-dichloro-4′-nitrophenyl), which was obtained in maximum amount after interaction of the above naphthaquinone derivative with aqueous sodium hydroxide for 10 minutes. The sodium sulphonate was hydrolysed to give (IV; R = 2′ : 6′-dichloro-4′-nitrophenyl) (39%). Compound (II; R = 2′ : 6′-dichloro-4′-nitrophenyl) was present in the mixed sodium sulphonates after reaction in the sodium hydroxide for 20 minutes, and with more prolonged reaction the proportion of it increased rapidly, with consequent diminution in amount of the isomeride (I).

Sodium 1-(2′-bromo-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate possessed similar stability in aqueous sodium hydroxide to the 2′-chloro-4′-nitro-compound, but was much less stable than the 2′ : 6′-dichloro-4′-nitro-analogue. After reacting for 15 seconds in sodium hydroxide, the β-naphthaquinone compound gave a mixture of (I and II; R = 2′-bromo-4′-nitrophenyl) in the approximate proportions of 1 : 2.

Bromine atoms in the 2′ : 6′-positions rendered sodium 1-(2′ : 6′-dibromo-4′-nitrophenyl)-β-naphthaquinone-1-sulphonate almost as stable to sodium hydroxide as the 2′ : 6′-dichloro-analogue, and the resultant compound (I; R = 2′ : 6′-dibromo-4′-nitrophenyl) was somewhat less stable than the 2′ : 6′-dichloro-compound.

Sodium 1-(4′-nitro-2′-methylphenyl)-β-naphthaquinone-1-sulphonate approximated in stability in sodium hydroxide to the 2′-chloro-4′-nitro-analogue, but the resultant compound (I; R = 4′-nitro-2′-methylphenyl) was less stable than the 2′-bromo-4′-nitro-analogue, although much more stable than the 4′-nitro-derivative.

The behaviour of sodium 1-(3′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate was exceptional. The ring was opened extremely readily and even after the minimum time for mixing with the sodium hydroxide (15 seconds), very little 3′-nitrobenzeneazo-β-naphthol was formed. There was immediate formation of (II; R = 3′-nitrophenyl) with no trace of the isomeride (I) as was proved by hydrolysis and fractional crystallisation of the product, which consisted of (V; R = 3′-nitrophenyl) only.

Experimental.

2-(4′-*Nitrophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 4′-nitrophenyl).—*p*-Nitroaniline (55 g.) was converted into sodium 1-(4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe *et al.*, *J.*, 1926, 699). An ice-cold suspension of the latter compound was stirred for 15 minutes and then added to a solution of sodium hydroxide (80 g.) in water (160 c.c.). The deep crimson solution was well stirred and, after 15 seconds, was rapidly acidified with concentrated hydrochloric acid, ethyl acetate being used to control frothing. The mixture was made alkaline with sodium carbonate, boiled, and filtered from 4′-nitrobenzeneazo-β-naphthol (20 g.; 17·2%), and hydrochloric acid (300 c.c.) was added gradually to the boiling filtrate until the evolution of sulphur dioxide had ceased and reddish-brown crystals had formed (99 g.; 75·9%). The product was washed with hot water, dried, and fractionally crystallised from ethyl acetate. Compound (V; R = 4′-nitrophenyl) predominated. Each successive crop of crystals was tested by mixed m. p. determinations; the more soluble fractions consisted of (IV; R = 4′-nitrophenyl), which crystallised from ethyl acetate in pale yellow prisms, m. p. 254° (17 g.; 13%) (Found: C, 58·3; H, 4·0; N, 12·6. $C_{16}H_{13}O_5N_3$ requires C, 58·7; H, 4·0; N, 12·8%).

2-(4′-*Nitrophenylamino*)iso*indolinone*-3-*acetic acid* dissolves in cold aqueous sodium carbonate and hydroxide with orange and orange-red colours, respectively.

The proportions of the compounds isolated under varied conditions and calculated as percentages on the weight of *p*-nitroaniline are tabulated below:

Time in sodium hydroxide (seconds).	Weight of sodium hydroxide used (g.).	4′-Nitrobenzeneazo-β-naphthol.	Compound (IV). (R = 4′-Nitrophenyl.)	Compound (V).
8	80	25	12	54
15	80	17	13	63
15	40	65	10	21

The *methyl* ester of compound (IV; R = 4′-nitrophenyl) crystallised from methyl alcohol in pale yellow needles, m. p. 166° (Found: C, 60·2; H, 4·55; N, 11·9. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%).

2 : 5-*Diketo*-3-(4′-*nitrophenyl*)iso*indolinopyrazolidocoline* (VI; R = 4′-nitrophenyl).—Finely powdered 2-(4′-nitrophenylamino)*iso*indolinone-3-acetic acid (10 g.) was boiled gently for 5 minutes with acetic anhydride (40 c.c.) and pyridine (2 c.c.) and cooled. The crystalline precipitate crystallised from acetic acid in almost colourless, prismatic needles, m. p. 250° (9·1 g.; 96·3%) (Found: C, 61·9; H, 3·6; N, 13·4. $C_{16}H_{11}O_4N_3$ requires C, 62·1; H, 3·55; N, 13·6%), insoluble in cold aqueous alkalis and dilute

mineral acids. Conversion of (IV; R = 4′-nitrophenyl) into the above *anhydro*-derivative (VI) was utilised as a means of separating it from the isomeride (V; R = 4′-nitrophenyl); the latter remains in acetic anhydride as the soluble acetyl derivative, and (VI) is deposited, indicating the amount of (IV) present in the mixture. The anhydro-compound is hydrolysed to (IV; R = 4′-nitrophenyl) by three methods.

(*a*) Concentrated hydrochloric acid (50 c.c.) was added to a boiling solution of (VI; R = 4′-nitrophenyl) (10 g.) in acetic acid (200 c.c.) during 15 minutes. After refluxing for a further 15 minutes, the mixture was concentrated to 100 c.c. and diluted with water (100 c.c.), and the precipitate was collected (9·7 g.; 91·7%).

(*b*) (VI; R = 4′-nitrophenyl) (10 g.) was added to a solution of potassium hydroxide (2·5 g.) in water (5 c.c.) and alcohol (25 c.c.), and the mixture was boiled until completely dissolved (3 min.), then cooled, diluted, and acidified (8·8 g.; 83·2%).

(*c*) (VI; R = 4′-nitrophenyl) (10 g.) was warmed with concentrated sulphuric acid (50 c.c.) at 70° for 3 minutes and the red solution poured on ice (400 g.). The precipitate was collected and extracted with aqueous sodium carbonate, and the solution acidified (7·4 g.; 70%).

2 : 5-*Diketo*-3-(4′-*aminophenyl*)*iso*indolinopyrazolidocoline.—Iron powder (2 g.) was added gradually to a boiling solution of finely powdered 2 : 5-diketo-3-(4′-nitrophenyl)*iso*indolinopyrazolidocoline (2·5 g.) in acetic acid (100 c.c.) and water (25 c.c.). After boiling until dilution with water gave no precipitate (10 minutes), the mixture was filtered (charcoal), cooled, partially neutralised with aqueous sodium carbonate, and shaken with excess of sodium chloride, and the liquid decanted and allowed to stand. Straw-coloured prisms of the amino-compound separated progressively and were filtered off after 0·5 hour, as subsequently a dark tar formed which hindered purification. This procedure was necessary in order to obtain the pure *base*, which crystallised from ethyl acetate in almost colourless prisms, m. p. 213—215° (1·6 g.; 70·9%) (Found: C, 68·95; H, 4·8; N, 15·1. $C_{16}H_{13}O_3N_3$ requires C, 68·8; H, 4·65; N, 15·05%). The *acetyl* derivative crystallised from alcohol in almost colourless needles, m. p. 263—264° (Found: C, 66·95; H, 5·0; N, 12·9. $C_{18}H_{15}O_4N_3$ requires C, 67·3; H, 4·7; N, 13·1%).

2-(2′-*Chloro*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 2′-chloro-4′-nitrophenyl).—An aqueous suspension of sodium 1-(2′-chloro-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate was prepared from 2-chloro-4-nitroaniline (52 g.) (Rowe and Dunbar, *J.*, 1932, 13), stirred, ice-cold, for 20 minutes, then added to sodium hydroxide (60 g.) in water (120 c.c.), stirred vigorously, and acidified after 45 seconds. After being made alkaline with sodium carbonate and filtered from 2′-chloro-4′-nitrobenzeneazo-β-naphthol (32 g.; 32·4%), the filtrate (charcoal) was cooled and carefully acidified with hydrochloric acid. Salt was added and, by next day, orange-yellow needles had formed (87 g.; 64·6%), consisting of sodium benzaldehyde 2′-chloro-4′-nitrophenylhydrazone-ω-sulphonate-2-β-acrylic acid, together with a little free sulphonic acid which could not be removed. The sodium sulphonate crystallised from ethyl acetate in golden-yellow needles, m. p. 225—227°, and the barium salt separated from hot water in similar coloured leaflets, m. p. 247°, but neither gave satisfactory analytical results, this being probably partially due to association of water. Hydrolysis of the sodium salt (25 g.) with boiling dilute hydrochloric acid (10 hours) gave 2-(2′-*chloro*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic acid*, which crystallised from ethyl acetate or aqueous acetic acid in pale orange prisms, m. p. 254° (18·5 g.; 91·6%) (Found: C, 52·9; H, 3·6; N, 11·05; Cl, 9·5. $C_{16}H_{12}O_5N_3Cl$ requires C, 53·1; H, 3·3; N, 11·6; Cl, 9·8%), soluble in aqueous sodium carbonate and hydroxide with orange and orange-red colours, respectively. Microscopical examination of these crystals, sprinkling on filter paper moistened with aqueous sodium carbonate, or fractional crystallisation from acetic acid (cf. Rowe *et al.*, *J.*, 1935, 1800), failed to reveal the presence of any benzo-2′-chloro-4′-nitrophenylhydrazone-2-β-acrylic acid (III; R = 2′-chloro-4′-nitrophenyl). When the time of reaction in the sodium hydroxide was varied, the following percentage yields were isolated:

Time in sodium hydroxide.	2′-Chloro-4′-nitrobenzeneazo-β-naphthol.	Compound (IV). (R = 2′-Chloro-4′-nitrophenyl.)	Compound (V).
15 seconds	66	23	nil
30 seconds	48	47	nil
45 seconds	32	61	nil
1 minute	28	59	6
2·5 minutes	24	43	18
10 minutes	27	7	54

The *methyl* ester of (IV; R = 2′-chloro-4′-nitrophenyl) crystallised from methyl alcohol in pale yellow needles, m. p. 144° (2·3 g.; 88·6%) (Found: C, 54·8; H, 4·25; N, 11·0; Cl, 9·4. $C_{17}H_{14}O_5N_3Cl$ requires C, 54·3; H, 3·7; N, 11·2; Cl, 9·45%).

2 : 5-*Diketo*-3-(2′-*chloro*-4′-*nitrophenyl*)iso*indolinopyrazolidocoline* (VI; R = 2′-chloro-4′-nitrophenyl).—(i) Prepared similarly to the 4′-nitro-analogue, this *base* crystallised from acetic acid in pale yellow, prismatic needles, m. p. 244° (9 g. from 10 g. of acid) (Found: C, 56·5; H, 3·2; Cl, 10·0. $C_{16}H_{10}O_4N_3Cl$ requires C, 55·9; H, 2·9; Cl, 10·3%), insoluble in cold aqueous alkalis, but soluble in hot sodium hydroxide with a deep crimson colour. It is hydrolysed best by method (*c*) used for the 4′-nitro-analogue (see above) (9·5 g. from 10 g.; 90·4%). (ii) 2-(2′-Chloro-4′-nitrophenylamino)*iso*indolinone-3-acetic acid (2 g.) was refluxed with phosphorus trichloride (3 c.c.) and dry toluene (400 c.c.) for 1 hour, and the mixture filtered and concentrated (1·5 g.; 78·9%).

2 : 5-*Diketo*-3-(2′-*chloro*-4′-*aminophenyl*)iso*indolinopyrazolidocoline* (VI; R = 2′-chloro-4′-aminophenyl).—Iron powder (4 g.) was added to a solution of (VI; R = 2′-chloro-4′-nitrophenyl) (5 g.) in acetic acid (160 c.c.) and water (40 c.c.), and the mixture boiled for 15 minutes, water (20 c.c.) being added during the reduction. The mixture was filtered (charcoal); the *amino*-compound which separated on standing crystallised from aqueous acetic acid in almost colourless, prismatic needles, m. p. 240° (3·9 g.; 85·5%) (Found: C, 61·0; H, 3·9; N, 13·0; Cl, 11·7. $C_{16}H_{12}O_3N_3Cl$ requires C, 61·2; H, 3·8; N, 13·4; Cl, 11·3%), or from aqueous alcohol in similar crystals containing 1 mol. of H_2O (Found: C, 59·6; H, 3·7; N, 12·8; Cl, 11·2. $C_{16}H_{12}O_3N_3Cl,H_2O$ requires C, 59·7; H, 4·0; N, 13·1; Cl, 11·0%).

It was stable to a hot solution of chromium trioxide in acetic acid. The *acetyl* derivative crystallised from alcohol in straw-coloured plates, m. p. 245° (Found: C, 60·5; H, 4·0; N, 11·8; Cl, 10·1. $C_{18}H_{14}O_3N_3Cl$ requires C, 60·8; H, 3·9; N, 11·8; Cl, 10·0%).

2-(2′-*Chloro*-4′-*aminophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 2′-chloro-4′-aminophenyl).—(*a*) Sodium hydrosulphite (20 g.) was added to a solution of 2-(2′-chloro-4′-nitrophenylamino)*iso*indolinone-3-acetic acid (10 g.) in sodium hydroxide (10 g.), water (300 c.c.) and alcohol (10 c.c.) at 80°, until the solution became pale yellow (alkaline). The mixture was filtered (charcoal), cooled, and carefully acidified with acetic acid until a precipitate began to form. The first deposits were rejected and the filtered solution allowed to stand; the amino-compound separated as an almost colourless amorphous precipitate (7·2 g.; 78·5%).

(*b*) Finely divided (IV; R = 2′-chloro-4′-nitrophenyl) (10 g.) was added rapidly to a boiling solution of stannous chloride (50 g.) in concentrated hydrochloric acid (125 c.c.). After boiling for 3 minutes, crystals began to separate. Concentrated hydrochloric acid (150 c.c.) was added and the mixture left over-night. The precipitate was filtered off, washed with cold concentrated hydrochloric acid and extracted with aqueous sodium carbonate, and the alkaline filtrate was neutralised with acetic acid (6·7 g.; 73·1%).

(*c*) Iron powder (6 g.) was added in portions, during 10 minutes, to a boiling solution of (IV; R = 2′-chloro-4′-nitrophenyl) (10 g.) in acetic acid (100 c.c.) and water (25 c.c.). The mixture was filtered (charcoal) and added to hot water (1 l.) to precipitate the base (4·8 g.; 52·3%).

(*d*) 2 : 5-Diketo-3-(2′-chloro-4′-aminophenyl)*iso*indolinopyrazolidocoline (VI; R = 2′-chloro-4′-aminophenyl) (10 g.) was dissolved in potassium hydroxide (7·5 g.), water (15 c.c.), and alcohol (75 c.c.) at 80° and the solution neutralised immediately with acetic acid (9 g.; 85%).

2-(2′-*Chloro*-4′-*aminophenylamino*)iso*indolinone*-3-*acetic acid* crystallised from aqueous alcohol n straw-coloured needles, m. p. 156—157° (decomp.), containing 1 mol. of H_2O (Found: C, 54·6; H, 4·9; N, 11·7; Cl, 10·1. $C_{16}H_{14}O_3N_3Cl,H_2O$ requires C, 54·95; H, 4·6; N, 12·0; Cl, 10·2%), removed by heating at 80° (Found: C, 57·2; H, 4·5; Cl, 10·2. $C_{16}H_{14}O_3N_3Cl$ requires C, 57·9; H, 4·2; Cl, 10·7%). It decomposes on prolonged boiling with organic solvents. On refluxing (5 g.) with boiling acetic anhydride (20 c.c.) and pyridine (1 c.c.), it was converted into 2 : 5-diketo-3-(2′-chloro-4′-acetamido)-*iso*indolinopyrazolidocoline, m. p. and mixed m. p. 245° (5·1 g.; 95·1%).

When a finely divided suspension of the base (IV; R = 2′-chloro-4′-aminophenyl) (2·5 g.) in cold dry toluene (150 c.c.) was refluxed, with stirring, and phosphorus trichloride (3 c.c.) added slowly, the suspension became gradually crystalline. After 10 minutes it was filtered off and extracted with cold aqueous sodium carbonate, and the residue crystallised from aqueous acetic acid in almost colourless, prismatic needles, m. p. and mixed m. p. 240°, of 2 : 5-diketo-3-(2′-chloro-4′-aminophenyl)*iso*indolinopyrazolidocoline.

2-(2′-Chloro-4′-aminophenylamino)*iso*indolinone-3-acetic acid was unchanged after refluxing with concentrated hydrochloric acid for 5 hours, by heating with the same reagent at 200° for 5 hours, or by refluxing with aqueous sulphuric acid, b. p. 140°, for 2 hours.

2-(2′ : 6′-*Dichloro*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 2′ : 6′-dichloro-4′-nitrophenyl).—2 : 6-Dichloroaniline (51·5 g.) was converted into sodium 1-(2′ : 6′-dichloro-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe, Dunbar, and Williams, *J.*, 1931, 1078), but excess of sodium β-naphthol-1-sulphonate was avoided, whereby subsequent filtration of the diazosulphonate, hitherto unduly slow with derivatives of dihalogeno-substituted anilines, was made easier.

The suspension of the β-naphthaquinone compound in sodium carbonate was stirred at 0° for 15 minutes, then added to sodium hydroxide (50 g.) in water (100 c.c.) and the deep crimson solution acidified after 10 minutes. 2′ : 6′-Dichloro-4′-nitrobenzeneazo-β-naphthol (45 g.; 50%) was filtered off and the sodium sulphonate in the filtrate was hydrolysed by boiling with hydrochloric acid. 2-(2′ : 6′-*Dichloro*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic acid* crystallised from acetic acid or ethyl acetate in pale yellow prisms, m. p. 203° (39 g.; 39·6%) (Found: C, 48·95; H, 3·1; N, 10·6; Cl, 18·45. $C_{16}H_{11}O_5N_3Cl_2$ requires C, 48·5; H, 2·8; N, 10·6; Cl, 17·9%), soluble in cold aqueous alkalis with a crimson colour.

Fractional crystallisation from ethyl acetate revealed no trace of 1-hydroxy-3-(2′ : 6′-dichloro-4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (V; R = 2′ : 6′-dichloro-4′-nitrophenyl), which was detected only after reaction of the β-naphthaquinone compound with sodium hydroxide for 20 minutes or longer, followed by hydrolysis in the usual manner. The following percentage yields were isolated after various periods of reaction in the sodium hydroxide:

Time in sodium hydroxide.	2′ : 6′-Dichloro-4′-nitrobenzeneazo-β-naphthol.	Compound (IV). (R = 2′ : 6′-Dichloro-4′-nitrophenyl.)	Compound (V).
15 seconds	96	nil	nil
1 minute	70	21	nil
10 minutes	50	39	nil
20 minutes	52	35	7
2 hours	48	9	30

The *methyl* ester of (IV; R = 2′ : 6′-dichloro-4′-nitrophenyl) crystallised from methyl alcohol in pale yellow needles, m. p. 180° (Found: Cl, 16·85. $C_{17}H_{13}O_5N_3Cl_2$ requires Cl, 17·3%).

2 : 5-*Diketo*-3-(2′ : 6′-*dichloro*-4′-*nitrophenyl*)iso*indolinopyrazolidocoline* (VI; R = 2′ : 6′-dichloro-4′-nitrophenyl).—Compound (IV; R = 2′ : 6′-dichloro-4′-nitrophenyl) (10 g.) was boiled gently with acetic anhydride (40 c.c.) and pyridine (2 c.c.) for 5 minutes. The *anhydro*-derivative crystallised from acetic acid in pale-yellow prismatic needles, m. p. 256° (9 g.; 94·3%) (Found: C, 50·8; H, 2·7; N, 11·2; Cl, 18·5. $C_{16}H_9O_4N_3Cl_2$ requires C, 50·8; H, 2·4; N, 11·1; Cl, 18·8%), insoluble in cold aqueous alkalis, but soluble in hot aqueous sodium hydroxide with a crimson colour. It (10 g.) was hydrolysed by boiling with hydrochloric acid (50 c.c.) and acetic acid (200 c.c.) for 15 minutes, concentrating, and diluting (9·5 g.; 90·8%).

2-(2′-*Bromo*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 2′-bromo-4′-nitrophenyl).—

2-Bromo-4-nitroaniline (54 g.) was converted into the β-naphthaquinone compound (Rowe, Jambuserwala, and Partridge, *J.*, 1935, 1135). The suspension of the latter was added to sodium hydroxide (50 g.) in water (100 c.c.), and the crimson solution acidified after 15 seconds. After removal of 2′-bromo-4′-nitrobenzeneazo-β-naphthol (66 g.; 71·3%), the filtrate was hydrolysed (22 g.; 21·8%). Fractional crystallisation from ethyl acetate gave 1-hydroxy-3-(2′-bromo-4′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (7 g.) and 2-(*2′-bromo-4′-nitrophenylamino*)iso*indolinone-3-acetic acid* (14 g.; 13·9%), the latter crystallising in almost colourless prisms, m. p. 259° (Found : C, 47·2; H, 3·2; N, 10·05. $C_{16}H_{12}O_5N_3Br$ requires C, 47·3; H, 3·0; N, 10·4%), soluble in aqueous sodium carbonate with an orange-red colour, becoming crimson on addition of sodium hydroxide. The *methyl* ester crystallised from methyl alcohol in pale yellow needles, m. p. 170° (Found : C, 48·6; H, 3·6; N, 10·5; Br, 19·3. $C_{17}H_{14}O_5N_3Br$ requires C, 48·6; H, 3·3; N, 10·0; Br, 19·05%).

2 : 5-*Diketo*-3-(2′-*bromo*-4′-*nitrophenyl*)iso*indolinopyrazolidocoline* (VI; R = 2′-bromo-4′-nitrophenyl).—Compound (IV; R = 2′-bromo-4′-nitrophenyl) (10 g.) gave, in the usual manner, almost colourless, prismatic needles of the *anhydro*-derivative, m. p. 272—273° (acetic acid) (9·2 g.; 96·2%) (Found : C, 49·5; H, 2·65; N, 10·95; Br, 20·25. $C_{16}H_{10}O_4N_3Br$ requires C, 49·5; H, 2·6; N, 10·8; Br, 20·6%), best hydrolysed to the acid by refluxing (10 g.) with concentrated hydrochloric acid (50 c.c.) and acetic acid (200 c.c.) for 15 minutes (9·4 g.; 89·7%).

2-(2′ : 6′-*Dibromo*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 2′ : 6′-dibromo-4′-nitrophenyl).—2 : 6-Dibromoaniline (59 g.) was converted into sodium 1-(2′ : 6′-dibromo-4′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe, Dunbar, and Williams, *loc. cit.*). After being kept ice-cold, with stirring, for 20 minutes, the suspension of the latter was added to sodium hydroxide (40 g.) in water (80 c.c.) and the deep crimson solution acidified after 1 minute. 2′ : 6′-Dibromo-4′-nitrobenzeneazo-β-naphthol (61 g.; 67·8%) was removed and hydrolysis of the sodium sulphonate gave almost pure 2-(2′ : 6′-*dibromo*-4′-*nitrophenylamino*)iso*indolinone*-3-*acetic acid*. It crystallised from ethyl acetate or aqueous acetic acid in pale yellow prisms, m. p. 232° (26 g.; 26·8%) (Found : C, 40·4; H, 2·3; N, 8·8; Br, 32·6. $C_{16}H_{11}O_5N_3Br_2$ requires C, 39·6; H, 2·5; N, 8·7; Br, 33·0%), soluble in aqueous alkalis with a crimson colour. Compound (V; R = 2′ : 6′-dibromo-4′-nitrophenyl) was not formed until after the reaction with sodium hydroxide had proceeded for 2—3 minutes. The following percentage yields were isolated after various periods of reaction in the sodium hydroxide:

Time in sodium hydroxide.	2′ : 6′-Dibromo-4′-nitrobenzeneazo-β-naphthol.	Compound (IV). (R = 2′ : 6′-Dibromo-4′-nitrophenyl.)	Compound (V).
15 seconds	88	8	nil
1 minute	68	27	nil
2·5 minutes	50	31	7
10 minutes	54	12	23
2 hours	55	3	32

The *methyl* ester of (IV; R = 2′ : 6′-dibromo-4′-nitrophenyl) crystallised from methyl alcohol in pale-yellow needles, m. p. 168° (Found : C, 41·25; H, 2·8; N, 7·9; Br, 32·5. $C_{17}H_{13}O_5N_3Br_2$ requires C, 40·9; H, 2·6; N, 8·4; Br, 32·1%).

2 : 5-*Diketo*-3-(2′ : 6′-*dibromo*-4′-*nitrophenyl*)iso*indolinopyrazolidocoline* (VI; R = 2′ : 6′-dibromo-4′-nitrophenyl).—Compound (IV; R = 2′ : 6′-dibromo-4′-nitrophenyl) (10 g.) gave the *anhydro*-compound (VI), which crystallised from acetic acid in pale yellow, prismatic needles, m. p. 290° (9 g.; 93·4%) (Found : C, 41·25; H, 2·0; N, 9·1. $C_{16}H_9O_4N_3Br_2$ requires C, 41·1; H, 1·9; N, 9·0%). It was hydrolysed similarly to the 2′-bromo-4′-nitro-analogue (89·2%).

2-(4′-*Nitro*-2′-*methylphenylamino*)iso*indolinone*-3-*acetic Acid* (IV; R = 4′-nitro-2′-methylphenyl).—3-Nitro-*o*-toluidine (50 g.) was converted into sodium 1-(4′-nitro-2′-methylbenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe and Siddle, *J.*, 1932, 476); this by interaction in the usual manner with sodium hydroxide (66 g.) in water (140 c.c.) for 15 seconds, gave 4′-nitro-2′-methylbenzeneazo-β-naphthol (64 g.; 63·5%) and a mixture of compounds (I and II; R = 4′-nitro-2′-methylphenyl). Hydrolysis of this mixture and fractional crystallisation of the product from ethyl acetate gave 2-(4′-*nitro*-2′-*methylphenylamino*)iso*indolinone*-3-*acetic acid*, which crystallised in pale yellow prisms, m. p. 238° (16 g.; 14·3%) (Found : C, 60·2; H, 4·7; N, 12·15. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%), soluble in aqueous sodium carbonate and hydroxide with orange-red and crimson colours, respectively. The *methyl* ester crystallised from methyl alcohol in pale yellow needles, m. p. 147° (Found : C, 60·6; H, 5·0; N, 12·15. $C_{18}H_{17}O_5N_3$ requires C, 60·85; H, 4·8; N, 11·8%).

2 : 5-*Diketo*-3-(4′-*nitro*-2′-*methylphenyl*)iso*indolinopyrazolidocoline* (VI; R = 4′-nitro-2′-methylphenyl) crystallised from acetic acid in pale yellow, prismatic needles, m. p. 213—214° (9 g. from 10 g. acid; 95%) (Found : C, 63·1; H, 4·1; N, 12·5. $C_{17}H_{13}O_4N_3$ requires C, 63·2; H, 4·0; N, 13·0%), hydrolysed best (89%) by a mixture of hydrochloric and acetic acids.

Derivatives of m-*Nitroaniline.*—*m*-Nitroaniline (55 g.) was converted into sodium 1-(3′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate (Rowe, Himmat, and Levin, *J.*, 1928, 2558). When the latter reacted with sodium hydroxide (80 g.) in water (160 c.c.) for 15 seconds, two products only were formed, *viz.*, 3′-nitrobenzeneazo-β-naphthol (11 g.; 9·4%) and sodium hydrogen 3-(3′-nitrophenyl)-3 : 4-dihydrophthalazine-1-sulphonate-4-acetate (130 g.; 78·9%), the latter being hydrolysed to (V; R = 3′-nitrophenyl). No trace of the isomeride (IV) was detected. The *acetyl* derivative of compound (V; R = 3′-nitrophenyl) crystallised from aqueous acetic acid or aqueous alcohol in pale yellow prisms, m. p. 175° (Found : C, 58·5; H, 4·3; N, 11·5. $C_{18}H_{15}O_6N_3$ requires C, 58·5; H, 4·1; N, 11·4%), soluble in aqueous sodium carbonate and hydroxide with golden-yellow and crimson colours, respectively.

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94. *Nitration in Sulphuric Acid. Part IV. Kinetics of the Nitration of 2 : 4-Dinitrotoluene.*

By G. M. Bennett, J. C. D. Brand, D. M. James, T. G. Saunders, and Gwyn Williams.

Velocities of nitration of 2 : 4-dinitrotoluene have been measured in media varying from 87·4% aqueous sulphuric acid to oleum containing 29·1% of free sulphur trioxide and at temperatures from 60° to 120°. The effects of varying initial concentrations, of variation of the composition of the medium and of additions of potassium bisulphate and nitrosyl bisulphate have been studied in detail.

In any one experiment it is confirmed that the bimolecular coefficient remains constant. The accompanying oxidation reaction is shown to be a simultaneous side reaction of the same order.

The process is regarded as involving attack by the NO_2^+ ion and a proton acceptor simultaneously, the actual proton-accepting species being HSO_4^-, H_2SO_4, and $HS_2O_7^-$. A general equation is developed in the form

$$d[TNT]/dt = \{k[HSO_4^-] + k'[H_2SO_4] + k''[HS_2O_7^-]\}[DNT][HNO_3]Q$$

where k, k', and k'' are coefficients relating to the action of the three proton-acceptors, respectively, and $Q = [NO_2^+]/[HNO_3]$ and is calculable from the ionic equilibria in solution. This is valid at a given temperature for all variations of medium. The constants of this equation have been determined for the temperature 89·9° and it is shown that the experimental results are adequately reproduced by it; in particular, the composition of the medium giving a maximum velocity of nitration is calculated in good agreement with that observed, namely, 92% H_2SO_4.

The constants of the Arrhenius equation have been calculated for the reaction.

In Part I of this series (Bennett, Brand, and Williams, *J.*, 1946, 869) evidence has been presented in support of the view that nitric acid dissolved in sulphuric acid is largely present as the NO_2^+ ion, and that this is the active nitrating agent in such mixtures.

The hypothesis of nitration by the NO_2^+ ion is thus particularly applicable to nitration in sulphuric acid solutions, and conveniently measurable velocities of nitration in such media are found only for aromatic substances such as nitrobenzene and dinitrotoluene containing deactivating substituents. The speed of nitration of benzene or of aromatic substances, such as phenol, containing activating substituents is too great in sulphuric acid for measurement. The nitration of compounds of the latter type has been studied in other solvents, but a comparison of the mechanisms of nitration for the same compound in solvents of different character presents difficulties.

Nitration in sulphuric acid is both faster and simpler than in other media for which quantitative data are available (perchloric acid as a medium is a probable exception, cf. Robinson, *J.*, 1941, 238). In other solvents, the rate of nitration is generally a complicated function of the reactant concentrations, which often appear raised to high powers in the kinetic equations; nitration is subject to positive or negative catalysis by nitrous acid; and the symptoms suggest that chain reactions may be involved, propagated, possibly, by free radicals. Examples are furnished by the nitration of benzene, toluene, ethylbenzene, and monohalogenobenzenes in nitromethane (Benford and Ingold, *J.*, 1938, 929), by the nitration of benzene in acetic anhydride (Cohen and Wibaut, *Rec. Trav. chim.*, 1935, **54**, 409), by the nitration of various aromatic compounds in nitrobenzene (Giersbach and Kessler, *Z. physikal. Chem.*, 1888, **2**, 676; Tronov and Ber, *J. Russ. Phys. Chem. Soc.*, 1930, **62**, 2337), and, notably, by the nitration of phenol in water and in organic solvents (*e.g.*, Martinsen, *Z. physikal. Chem.*, 1904, **50**, 385; Arnall, *J.*, 1923, **123**, 3111; Klemenc and Schöller, *Z. anorg. Chem.*, 1924, **141**, 231; Kartashev, *J. Russ. Phys. Chem. Soc.*, 1930, **62**, 2129; Veibel, *Z. physikal. Chem.*, 1930, *B*, **10**, 22; *Ber.*, 1930, **63**, 1557, 1582, 2074). In sulphuric acid–water media, the speed of nitration is greatly affected by the proportion of water present; and Martinsen (*loc. cit.*; *ibid.*, 1907, **59**, 605) found that nitration of a number of substituted benzenes in homogeneous solution is fastest in a slightly aqueous sulphuric acid (*ca.* 90% H_2SO_4 at 25° whatever the substance nitrated), becoming slower both in anhydrous sulphuric acid (or oleum) and in media with a higher water content than the optimum. Martinsen's discovery has since been confirmed for the nitration of substituted xylenes (Klemenc and Schöller, *loc. cit.*), of anthraquinone (Lauer and Oda, *J. pr. Chem.*, 1936, **144**, 176) and substituted anthraquinones (Oda and Ueda, *Bull. Inst. Phys. Chem. Res. Japan*, 1941, **20**, 335; *A.*, 1942, II, 58), and of naphthalenesulphonic acids (Lantz, *Bull. Soc. chim.*, 1939, **6**, 280, 289, 302). But in a sulphuric acid medium of given water content, there has been general agreement that nitration is a second-order reaction, not catalytically affected by the presence of nitrous acid or of phosphoric oxide.

The rapidity and kinetic simplicity of nitrations in sulphuric acid, compared with other media, are consistent with the view that nitration in sulphuric acid is ionic; and we have identified the NO_2^+ ion as the active nitrating agent in mixed acids, but the assumption of an ionic nitrating agent does not, by itself, explain why 90% sulphuric acid is an optimum medium. It has been suggested (Lauer and Oda; Lantz; *locc. cit.*) that a nitric acid cation is responsible for nitration in anhydrous sulphuric acid only and that the $NO_2{\cdot}OH$ molecule is the nitrating agent in more aqueous media. This view is not tenable for the nitration of such substances as dinitrotoluene because the reaction is negligibly slow in the medium (having a molar ratio $H_2O/H_2SO_4 = 1$) in which the concentration of molecular nitric acid, $NO_2{\cdot}OH$, is greatest, as Hetherington and Masson have convincingly proved for the nitration of nitrobenzene in two-phase systems (*J.*, 1933, 105). Assuming that the NO_2^+ ion is the most active nitrating agent in all media in which nitration has a measurable speed for substances of this type, an alternative explanation for the optimum medium at 90% H_2SO_4 can be found if it is recalled that nitration requires, not only the attachment of the cation to the benzene nucleus, but also the removal of a proton, provided that it be assumed that the speed of nitration depends upon both factors (cf. Robinson, " Outline of an Electrochemical Theory of the Course of Organic Reactions," Institute of Chemistry, 1932; *J.*, 1941, 238; we are indebted to Sir Robert Robinson, P.R.S., who personally suggested to us in 1942 that the composition of the medium in which the velocity of nitration is a maximum might represent a balance between the acid function of the solvent and its basic function as a proton-acceptor). The most obvious proton-acceptor in a sulphuric acid–water mixture (in which the molar ratio $H_2O/H_2SO_4 < 1$) is the bisulphate ion, though the sulphuric acid molecule is probably also effective to a lesser degree. Increase in the water content of the medium (causing increased bisulphate-ion concentration) increases the facility with which a proton can be removed from the organic compound; but it also reduces the concentration of the NO_2^+ ion, the active nitrating agent. A balance of these two effects leads to the observation of a maximum rate of nitration in a slightly aqueous medium. This theory is formulated quantitatively in a later section of this paper. Its immediate consequences are: (*a*) addition of bisulphate ion—as metallic salt, as nitrosyl bisulphate (nitrous acid), or in any other form—should accelerate nitration in a medium containing more sulphuric acid, and retard it in media containing more water, than the optimum composition; (*b*) since nitric acid forms bisulphate ion when it is dissolved in concentrated sulphuric acid, the bimolecular velocity coefficients recorded for individual nitrations should rise with increasing initial nitric acid concentration in media on the acid side of the optimum and should fall with increasing nitric acid in media on the water side of the optimum. Lauer and Oda (*loc. cit.*) have observed that metallic nitrates nitrate anthraquinone more rapidly than does nitric acid in sulphuric acid media; Westheimer and Kharasch also give evidence of these effects (*J. Amer. Chem. Soc.*, 1946, **68**, 1871). Existing data, however, cover too narrow a range of conditions to be conclusive. In order to test the theory of nitration by an ion, we have therefore investigated the kinetics of nitration over as wide a range of conditions as possible. The anticipated effects have been observed with the four compounds so far examined. The present paper deals with 2 : 4-dinitrotoluene; other substances will be considered in later papers.

The Nitration of 2 : 4-*Dinitrotoluene.*—The nitration of 2 : 4-dinitrotoluene (referred to hereafter as DNT) to 2 : 4 : 6-trinitrotoluene (TNT) is accompanied by oxidation processes, which have been investigated by A. Carruthers and L. A. Wiseman. We are indebted to them for permission to refer to some of their unpublished results. They find that the main detectable products of the oxidation reactions are nitrous acid and equal volumes of carbon monoxide and carbon dioxide. The gases are formed by oxidation of DNT, which suffers complete nuclear disruption, so that the loss of one molecule of DNT gives rise to the production of many molecules of nitrous acid. In preparative nitration, some 3% of DNT is oxidised at 90°. Our experiments have been conducted on homogeneous solutions, composed of small concentrations of DNT and nitric acid (0·05—0·8M) in media containing varying proportions of sulphuric acid and water. The sulphuric acid and water components of the nitrating acid are then present in large excess and can be regarded as forming a constant medium for the nitration. For example, in an experiment in 95·7% sulphuric acid, the initial composition of the system was as follows:

DNT:	0·04 mole	HNO_3:	0·02 mole (0·7% by weight of nitrating acid)
H_2SO_4:	1·8 mole	H_2O:	0·44 mole

The amounts of water and nitrous acid formed during nitration are too small to affect the

composition of the system and the rate of nitration appreciably, especially as attention is confined to the early stages of nitration (generally up to not more than 30% conversion of DNT).

Under these conditions, at 90°, some 40% of the total nitric acid consumed appears as nitrous acid, but the amount of DNT consumed in oxidation is negligibly small compared with that consumed in nitration, provided that DNT is initially present in excess over nitric acid. This has been proved by direct analyses of the mixed nitro-compounds isolated from the reaction mixture (by a determination of the density at 90° and by reference to a density–composition curve) and by comparing the extent of conversion of DNT into TNT so deduced with that deduced from acid analyses. The results of these experiments are shown in Table XI and are discussed in the Experimental section. So long as the proportion of DNT oxidised is small, acid analyses will suffice to separate the nitration reaction from the oxidation; and the rate of nitration may be determined in the following way.

Nitration of DNT takes place, at a fixed temperature (generally 90°), in homogeneous solution in sulphuric acid mixed with a known proportion of water or sulphur trioxide. Samples of reaction mixtures are withdrawn at known time intervals, in pipettes calibrated for the prevailing conditions. Alternate samples are analysed for nitric acid, by electrometric titration with standard ferrous sulphate solution, and for nitrous acid, by oxidation with standard chloramine-T or ceric sulphate solutions. These results give (*a*) the total amount of nitric acid consumed in both nitration and oxidation, and (*b*) the amount of nitric acid consumed in oxidation alone. The amount of nitric acid consumed in nitration can therefore be deduced. This quantity is equated to the amount of TNT formed, a procedure which is justified by the results of Table XI. The velocity coefficient for nitration is derived by taking rates of nitration at known times directly from a curve drawn to represent the increase of TNT concentration with time, and substituting in the differential equation (1). The curves for a pair

$$d[TNT]/dt = k_2[DNT][HNO_3] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

of duplicate experiments are shown in Fig. 1. The derived velocity coefficients for one of them are given below.

Experiment 205.

Medium, 98·7% H_2SO_4. Temp., 89·9°. Initial concn.: DNT = 0·4007M, HNO_3 = 0·2004M

Time (mins.).	Reaction, %.	DNT converted, %.	[TNT]/[HNO_3].	$k_2 \times 1000$.
10	5·8	1·8	1·5	9·4
20	11·6	3·6	1·6	10·4
30	17·2	5·4	1·6	10·8
40	22·5	7·0	1·6	10·7
50	27·5	8·5	1·6	11·3
60	32·1	9·9	1·6	10·4
70	36·5	11·2	1·6	10·8
80	40·5	12·4	1·6	10·7
90	44·3	13·5	1·6	10·9
100	47·7	14·5	1·6	10·9
110	50·8	15·4	1·5	10·5
120	53·7	16·2	1·5	10·0

In this, as in other experiments, the velocity coefficient remains constant during the course of nitration. In a given medium, therefore, and for fixed values of the initial concentrations, the rate of nitration is determined by equation (1). This result is in agreement with the findings of previous workers.

The reason for calculating nitration velocity coefficients from the differential form of equation (1) is that the integrated form cannot be used without making assumptions about the mechanism of the oxidation processes, since nitric acid is used up in oxidation without appreciable consumption of DNT. By making appropriate assumptions, an integrated form may be applied in the following manner.

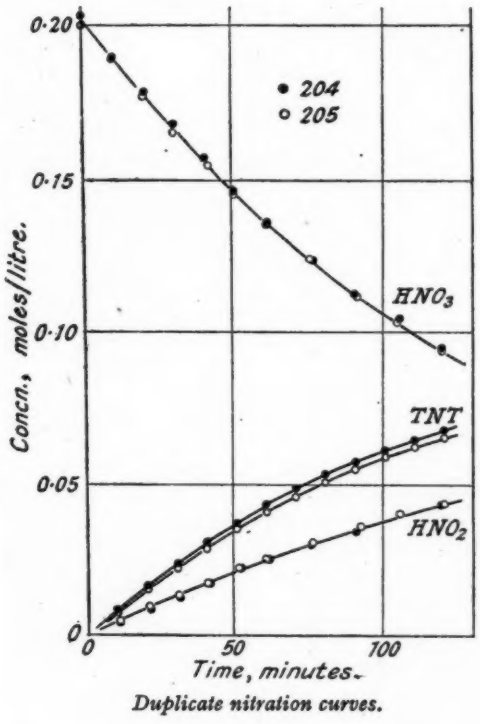
The Oxidation Reactions.—The chemical facts of oxidation, outlined on p. 475, and the kinetic conclusions about oxidation which may be inferred from the experimental results, are met by the supposition that a few molecules of DNT ultimately break up completely into fragments, which then react independently with nitric acid to form carbon monoxide, carbon dioxide, and nitrous acid. The kinetics require that the preliminary breakdown of DNT molecules should be the rate-determining step in this process. The mechanism may be treated formally in the following way.

Consider two simultaneous reactions :

(*a*) Nitration : $DNT + HNO_3 \longrightarrow TNT + H_2O$
(*b*) Breakdown of DNT : $DNT + HNO_3 \longrightarrow X_1 + X_2 + \ldots + X_i + \ldots + X_n$ + etc.

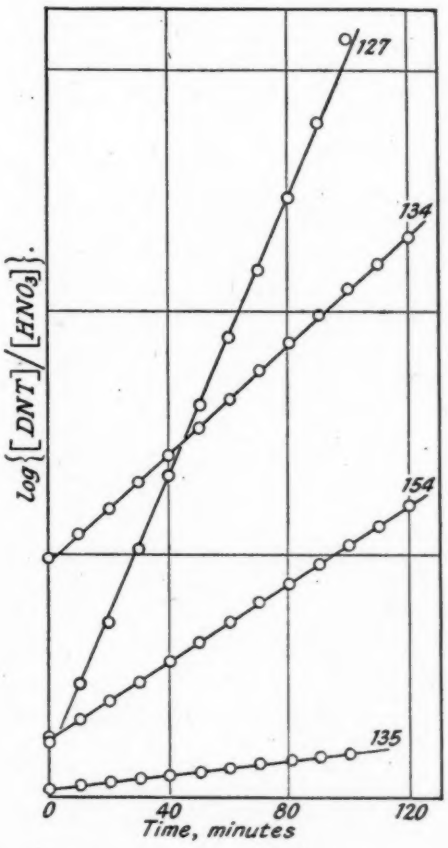
where the X_i are short-lived intermediate fragments, possibly free radicals.

FIG. 1.



Duplicate nitration curves.

FIG. 2.



Let the velocity coefficients of reactions (*a*) and (*b*) be k_a and k_b respectively. The intermediates X_i react with nitric acid in a series of parallel, independent reactions, typified by equation (i).

$$[X_i] + HNO_3 \longrightarrow HNO_2 + \text{etc.} \quad \text{Velocity coeff.} : k_i \quad . \quad . \quad . \quad . \quad \text{i)}$$

Applying the condition $d[X_i]/dt = 0$, we find :

$$[X_i] = (k_b/k_i)[DNT]$$

and
$$d[HNO_2]/dt = [HNO_3]\sum_1^n k_i[X_i] = nk_b[DNT][HNO_3]$$

so that
$$\frac{d[TNT]/dt}{d[HNO_2]/dt} = \frac{k_a}{nk_b} = \text{Const.}$$

Integrating, with the condition $[TNT] = 0 = [HNO_2]$ when $t = 0$,

$$[TNT]/[HNO_2] = k_a/nk_b = \text{Const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

This conclusion is in accord with experiment.* The ratio $[TNT]/[HNO_2]$ remains constant

* If nitrous acid is taken to be formed in reaction (*b*), as well as in (i), n in equation (2) becomes $n + 1$. The argument is unaffected.

during nitration or drifts with time only over a small range; and its mean value in a given nitration is insensitive to any change of experimental conditions other than temperature (see Tables II—IV, etc.). The experimental constancy of the ratio [TNT]/[HNO_2] seems sufficiently exact to warrant the inference that Wegscheider's test (*Z. physikal. Chem.*, 1899, **30**, 593) for simultaneous side reactions is approximately fulfilled, which implies that the rate-determining steps in oxidation and nitration of DNT are *simultaneous side reactions of the same order*. Thus the rate of formation of nitrous acid must depend on the DNT concentration, even though the amount of DNT consumed by oxidation is small compared with the amount of nitrous acid formed. The formation of nitrous acid must therefore involve consecutive steps.

The experimentally verified conclusion of equation (2) is satisfied by the following empirical formulation : Let initial concentrations of DNT and HNO_3 be a and b, respectively. Let concentrations of TNT and HNO_2 formed at time t be x and y, respectively.

$$\text{Put } x/y = s \text{ and } (s + 1)/s = r$$

Then
$$y = x/s \text{ and } [\text{DNT}]/[\text{HNO}_3] = (a - x)/(b - rx)$$
$$\mathrm{d}x/\mathrm{d}t = k_a(a - x)(b - x - y) \text{ and } \mathrm{d}y/\mathrm{d}t = nk_b(a - x)(b - x - y)$$

and
$$r \,.\, \mathrm{d}x/\mathrm{d}t = (k_a + nk_b)(a - x)(b - rx)$$

which gives, on integration

$$(k_a + nk_b)t = \frac{2{\cdot}3r}{ar - b} \log_{10} \left\{ \frac{b}{a} \cdot \frac{a - x}{b - rx} \right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

It follows that the plot of $\log_{10}$ [DNT]/[HNO_3] against t should be a straight line of slope l, where

$$k_a = (k_a + nk_b)/r = l \times 2{\cdot}3/(ar - b)$$

This conclusion is verified experimentally. Fig. 2 shows that $\log_{10}$ [DNT]/[HNO_3] is a linear function of time for a number of nitrations. This means, *as an empirical result*, that the rate of reaction is expressed by an integrated bimolecular equation; and the test represented by Fig. 2 has a wider implication than the test based on constancy of the bimolecular nitration velocity coefficient (Expt. 205 above). It means that the rate of consumption of DNT and HNO_3 in both oxidation and nitration follows a bimolecular course, since it is the quotient of total concentrations of DNT and nitric acid which is used in the plot. If the particular oxidation mechanism postulated has any approach to reality, then the velocity coefficient k_a for nitration, derived from the slope l should be identical with k_2, the nitration velocity coefficient calculated from the differential equation (1) as described on p. 476.

A comparison of k_2 (from the *differential* equation 1) with k_a (from the *integrated* equation 3) is made in Table I.

TABLE I.

Comparison of k_2 *with* k_a.

Expt. No.	Medium : % H_2SO_4.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	10^3k_a.	10^3k_2.
154	89·5	0·3984	0·1992	17·3	17·0
134	95·1	0·4008	0·1014	18·4	17·2
126	95·1	0·4011	0·2019	19·2	18·3
137	95·1	0·4002	0·3013	20·3	18·8
130	95·1	0·1000	0·2019	17·2 *	13·8
127	95·1	0·8017	0·2062	23·6	21·5
103	100	0·6014	0·1991	9·5	8·7

* Value unreliable, because $ar \sim b$.

In general, k_a is some 5—10% higher than k_2 as given in Tables II—IV, etc. The discordance is not surprising. The highly formalised mechanism outlined above cannot be exactly true. Experimentally, also, the ratio s (*i.e.*, [TNT]/[HNO_2]) is not very accurately determined. The object of this discussion is merely to define a *type* of mechanism which shall be consistent with the observed products and kinetics of the reaction. For these reasons, velocity coefficients for nitration have always been calculated directly from the differential

equation (1), as described on p. 476. The coefficients calculated in this way give a more direct measure of the speed of nitration and do not involve the ratio $[TNT]/[HNO_2]$.

Results.—The results of all velocity measurements are collected in Tables II—V, VIII, and IX. For all experiments, concentrations are expressed in moles/litre and time is in minutes.

TABLE II.

Influence of medium on rate of nitration (Temp. 89·9°).

Medium. Wt. % of H_2SO_4.	Acid No.	Medium. $\frac{H_2O}{H_2SO_4}$.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_2, M.	$\frac{[TNT]}{[HNO_2]}$.	10^3k_2.
100	16	0	Table III : 99, 100, 101, 208			1·6	7·4
99·3	6	0·039	15	0·398	0·193	1·5	8·5
99·2	15	0·046	Table IV : 80, 86			1·4	8·6
98·7	34	0·075	204	0·4000	0·2032	1·8	10·8
98·7	34	0·075	205	0·4007	0·2004	1·6	10·6
97·8	32	0·120	200	0·4005	0·2016	1·7	11·0
97·8	32	0·120	201	0·4001	0·2006	1·6	10·8
97·7	35	0·128	206	0·4005	0·2005	1·5	12·3
97·7	35	0·128	207	0·4004	0·2016	1·7	12·5
96·5	33	0·197	202	0·4000	0·2000	1·8	15·0
96·5	33	0·197	203	0·4005	0·2007	1·6	14·4
95·1	20	0·285	Table III : 125, 126, 145			1·5	18·8
95·0	21	0·277	Table III : 146, 152			1·5	19·2
94·7	C	0·305	120	0·4001	0·1932	1·6	19·5
94·7	C	0·305	121	0·4005	0·2007	1·6	19·7
93·8	D	0·360	113	0·4000	0·1961	1·5	21·5
93·0	D	0·410	115	0·4010	0·2161	1·8	22·5
92·6	B	0·435	109	0·4013	0·2000	1·5	23·5
92·5	D	0·442	117	0·4010	0·2133	1·9	23·5
92·3	C	0·454	122	0·4008	0·1939	1·6	23·8
92·0	B	0·470	110	0·4012	0·2008	1·5	24·1
91·9	D	0·480	114	0·4006	0·2001	1·6	24·3
91·9	D	0·480	119	0·4012	0·2041	1·8	23·2
91·7	A14	0·495	76	0·4012	0·1960	1·9	23·6
91·7	A14	0·495	94	0·4012	0·2034	1·7	22·9
91·4	D	0·512	116	0·4019	0·1963	1·8	22·2
91·0	D	0·538	118	0·4012	0·2003	1·9	20·5
91·0	C	0·538	123	0·4004	0·2004	1·8	21·4
89·5	22	0·636	154	0·3984	0·1992	1·8	17·0
89·5	40	0·636	242	0·4004	0·2008	1·7	16·7
89·3	12	0·653	88	0·4010	0·2061	2·0	16·2
89·3	10	0·655	Table IV : 49, 51			1·8	16·0
87·6	43	0·770	287	0·3990	0·2000	1·6	6·9
87·6	43	0·770	290	0·4000	0·2002	1·3	6·3
87·4	11	0·788	53	0·4012	0·1909	1·5	7·2
87·4	11	0·788	55	0·4009	0·1920	1·5	6·7

Note.—In order to determine a number of points in the region of the maximum, an acid of known composition, differing slightly from that of the optimum acid, was taken as standard; and known weights of water were introduced in individual nitrations. The various series of acid compositions obtained in this way are those indicated by letters in Table II.

For a given temperature, the results may be summarised as follows :

Influence of medium composition. With fixed initial concentrations of the reactants (0·4M-DNT and 0·2M-HNO_2) the rates of nitration have been measured in media ranging in composition from 87·4% sulphuric acid (with water) to 29·1% sulphur trioxide in sulphuric acid (see Tables II and VIII). The nitration velocity coefficient has a maximum value in a medium composed of 92% sulphuric acid and 8% water (compare Fig. 3). This composition is frequently referred to below as the " optimum composition ".

Influence of reactant and bisulphate concentrations (Tables III—V). The observed facts are :

(1) *In media containing more sulphuric acid than the optimum composition.* The bimolecular velocity coefficient k_2 *rises* (*a*) with rising initial concentration of nitric acid (for a fixed initial concentration of DNT), (*b*) with rising initial concentration of DNT (for a fixed initial concentration of nitric acid), (*c*) with rising concentration of bisulphate, added either as potassium bisulphate or as nitrosyl bisulphate (for fixed initial concentrations of both reactants). The conclusions (*a*) and (*b*) hold also for an oleum medium (Table VIII).

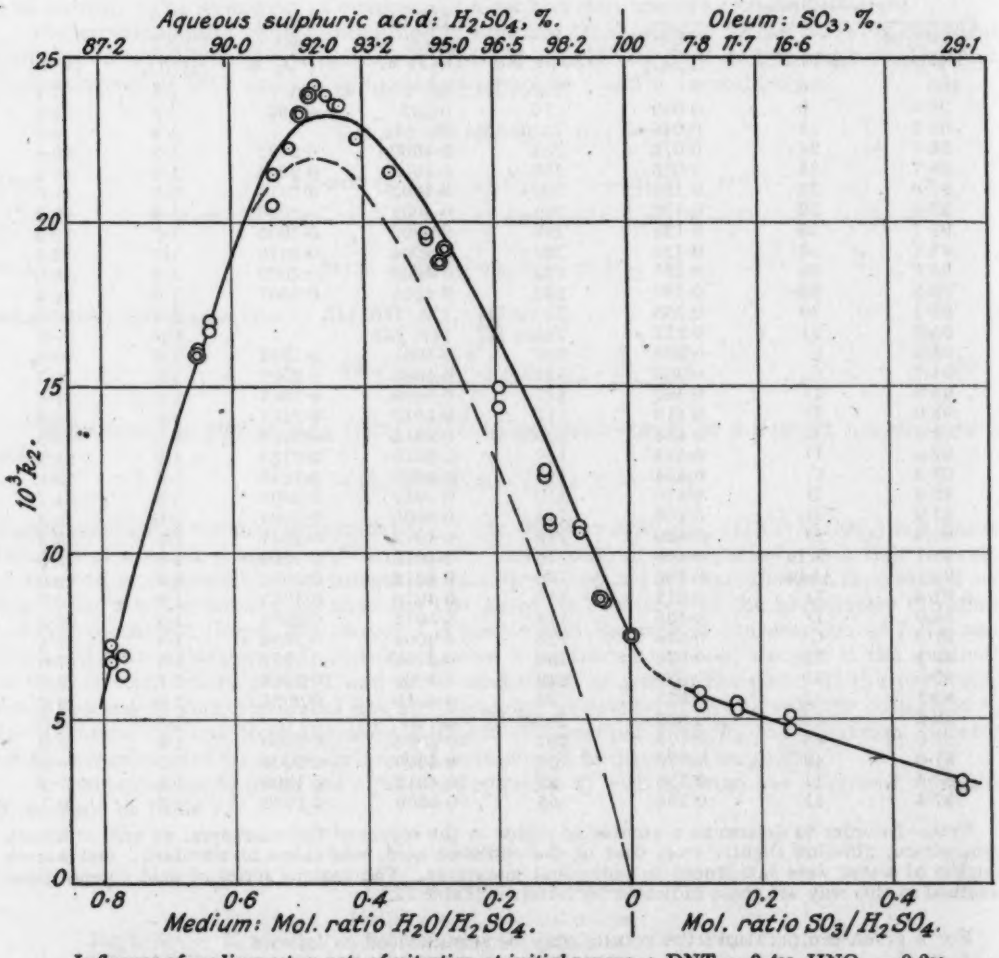
(2) *In media containing less sulphuric acid than the optimum composition.* The bimolecular

velocity coefficient k_2 *falls* (*a*) with rising initial concentration of nitric acid, (*b*) with rising initial concentration of DNT, (*c*) with rising concentration of added bisulphate.

In each instance, the relation between k_2 and reactant concentration is approximately linear over the range examined (Figs. 4 and 5).

It follows that the nitration of DNT to TNT is not really a second-order reaction, despite the constancy of k_2 observed in individual nitrations. Nevertheless, we have not tried to derive

FIG. 3.



Influence of medium upon rate of nitration at initial concns.: DNT = 0·4M, HNO_3 = 0·2M.

⊙ *Experimental points.* —— *Calculated curve of equation*

--- 1*st approximation.*

$$10^3k_2 = \frac{3{\cdot}3[HSO_4^-] + 0{\cdot}37[H_2SO_4]}{1 + \frac{[OH_3^+]}{33{\cdot}6}\left\{\frac{[HSO_4^-]}{[H_2SO_4]}\right\}^2} + 0{\cdot}56[HS_2O_7^-]$$

the formal order of reaction from the variation of nitration speed with initial concentrations of reactants, for the following reasons:

(1) The dependence of k_2 on initial concentration, though linear, is not a proportionality. Consequently, no integral order could represent the reaction.

(2) The sign of the variation of k_2 with initial concentration of either reactant is inverted when the medium composition is varied so as to pass through its optimum value. Any "order" deduced by formal methods would thus be different for media on either side of the optimum.

Variations of k_2 with initial nitric acid concentration and with added bisulphate concentration, of opposite sign in media on either side of the optimum composition, are required by the theory of nitration put forward below (compare p. 487). But the closely similar variation of k_2 with initial DNT concentration is unexpected and is not accounted for by the theory in its present form. The point is discussed further in a later section. Provisionally, the discussion which follows must be held to refer to a fixed initial concentration of DNT; and the experiments quoted in support of the postulated mechanism are all for 0·4M initial DNT.

TABLE III.

Variation of initial nitric acid concentration (Temp. 89·9°).

Medium.							
Wt. % H_2SO_4.	Acid No.	$\frac{H_2O}{H_2SO_4}$.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	$\frac{[TNT]}{[HNO_3]}$.	10^3k_2.
100	16	0	102	0·2006	0·1996	1·4	6·9
	,,	,,	97	0·2008	0·3859	1·6	8·0
	,,	,,	100	0·4014	0·1990	1·6	7·5
	,,	,,	99	0·4010	0·1984	1·6	7·1
	,,	,,	101	0·4022	0·1989	1·7	7·5
	31	0	208	0·3956	0·1994	1·6	7·4
	36	0	220	0·3998	0·2010	1·5	7·6
	16	0	95	0·4002	0·3883	1·4	8·2
	,,	,,	106	0·4011	0·8201	1·3	10·5
	,,	,,	104	0·6015	0·1991	1·7	8·5
	,,	,,	103	0·6014	0·1991	1·6	8·6
	,,	,,	98	0·5999	0·3865	1·9	10·6
	,,	,,	105	0·6024	0·8331	1·3	12·1
99·2	7	0·0395	35	0·198	0·0528	1·6	8·1
	6	0·039	21	0·195	0·0984	1·6	7·8
	6	,,	18	0·198	0·196	1·4	7·8
	6	,,	5	0·197	0·196	1·2	7·9
	6	,,	10	0·190	0·187	1·5	8·5
	6	,,	20	0·182	0·384	1·6	9·0
95·7	8	0·246	42	0·211	0·117	1·4	14·5
	8	,,	38	0·189	0·421	1·6	14·3
	8	,,	40	0·195	0·915	1·4	17·8
	28	,,	181	0·4001	0·6068	1·6	19·5
	28	0·243	182	0·4002	0·6038	1·1	19·9
	28	,,	183	0·4000	0·6040	1·9	19·8
95·1	20	0·285	131	0·4004	0·1015	1·4	17·2
	20	,,	134	0·4008	0·1014	1·6	17·2
	39	0·283	233	0·3989	0·2027	1·3	18·2
	20	0·285	125	0·4002	0·2082	1·4	18·6
	20	,,	126	0·4011	0·2019	1·5	18·3
	20	,,	145	0·4014	0·2038	1·6	19·4
	21	0·277	146	0·4009	0·2038	1·5	18·9
	21	,,	152	0·4008	0·2058	1·4	19·4
	20	0·285	137	0·4002	0·3013	1·5	18·8
	20	,,	132	0·4000	0·3999	1·5	18·4
	20	,,	133	0·4008	0·4116	1·5	18·2
	20	,,	139	0·4000	0·4026	1·5	19·8
	20	,,	143	0·4017	0·4156	1·5	20·1
	21	0·277	147	0·4008	0·4044	1·5	19·8
	20	0·285	136	0·4004	0·5125	1·5	19·6
	20		138	0·4011	0·5005	1·5	20·0
	20	,,	135	0·4008	0·6145	1·5	20·3
	20	,,	144	0·4006	0·5951	1·5	20·7
	21	0·277	148	0·4012	0·6160	1·6	20·7
	21	,,	153	0·4007	0·6031	1·45	19·7
89·5	22	0·636	160	0·4007	0·1008	1·8	18·2
	,,	,,	154	0·3984	0·1992	1·8	17·0
	,,	,,	159	0·4006	0·4002	1·7	15·6
	,,	,,	163	0·4001	0·4012	2·0	16·9
	,,	,,	162	0·4002	0·4964	1·8	16·0
	,,	,,	161	0·3997	0·5937	2·0	15·9

TABLE IV.

Variation of initial DNT *concentration* (Temp. 89·9°).

Medium.							
Wt. % H_2SO_4.	Acid No.	$\frac{H_2O}{H_2SO_4}$.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	$\frac{[TNT]}{[HNO_3]}$.	10^3k_2.
100	16	0	107	0·1003	0·1986	1·3	6·0
	,,	—	102	0·2006	0·1996	1·4	6·9
	,,	Table III, Average		0·400	0·199	1·6	7·4
	,,	Table III, Average		0·601	0·199	1·6	8·6
	,,	,,	97	0·2008	0·3859	1·6	8·0
	,,	,,	95	0·4002	0·3883	1·4	8·2
	,,	,,	98	0·5999	0·3865	1·9	10·6
	,,	,,	106	0·4011	0·8201	1·3	10·5
	,,	,,	105	0·6024	0·8331	1·3	12·1
99·2	6	0·039	19	0·102	0·197	1·4	7·4
	6	Table III, Average		0·195	0·193	1·4	8·0
	6	,,	15	0·398	0·193	1·5	8·5
	15	0·046	80	0·4011	0·2018	1·7	9·0
	15	,,	86	0·4011	0·1964	1·1	8·2
	6	0·039	17	0·525	0·190	1·4	9·1
	6	,,	4	0·302	0·315	1·4	9·3
95·7	8	0·246	44	0·100	0·186	1·6	14·1
	,,	,,	47	0·103	0·191	1·4	13·3
	,,	,,	43	0·385	0·207	1·6	14·9
	,,	,,	39	0·321	0·311	1·6	17·4
95·1	20	0·285	130	0·1000	0·2019	1·3	13·8
	20	,,	129	0·2003	0·2102	1·3	15·2
	20/21	Table III, Average		0·401	0·205	1·5	18·9
	20	0·285	128	0·6040	0·2079	1·5	19·5
	20	,,	127	0·8017	0·2062	1·5	21·5
89·5	22	0·636	157	0·1000	0·2005	2·0	19·8
	,,	,,	156	0·2503	0·1998	1·6	17·4
	,,	,,	154	0·3984	0·1992	1·8	17·0
	,,	,,	155	0·5977	0·2006	2·0	16·0
	,,	,,	158	0·8017	0·1987	1·7	14·3
89·3	10	0·655	52	0·200	0·186	1·6	16·5
	5	,,	12	0·200	0·223	1·8	16·6
	10	0·656	51	0·402	0·179	1·7	15·5
	10	,,	49	0·398	0·186	1·9	16·5
	12	0·653	88	0·4010	0·2061	2·0	16·2

TABLE V.

Influence of added bisulphates (Temp. 89·9°).

Medium.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	Added material. Subst.	Added material. Mols./l.	$\frac{[TNT]}{[HNO_3]}$.	10^3k_2.
99·3% H_2SO_4	Mean from Table IV			—	—	1·4	8·6
	28	0·400	0·199	$KHSO_4$	0·300	1·3	9·3
	32	0·401	0·187	$KHSO_4$	0·604	1·4	10·5
	11	0·199	0·191	$KHSO_4$	0·972	1·3	10·6
	34	0·401	0·0563	$KHSO_4$	1·000	1·55	11·1
	30	0·401	0·195	$KHSO_4$	1·002	1·2	11·4
	31	0·395	0·176	$KHSO_4$	1·476	1·4	14·0
	46	0·396	0·202	$NO{\cdot}HSO_4$	0·13	1·3	8·8
	45	0·408	0·177	$NO{\cdot}HSO_4$	0·16	1·2	9·0
	48	0·401	0·198	$NO{\cdot}HSO_4$	0·34	(1·6)	9·9
89·3% H_2SO_4	Mean from Table IV			—	—	1·9	16·1
	89	0·401	0·215	$KHSO_4$	0·195	2·0	12·2
	72	0·396	0·195	$KHSO_4$	0·196	1·35	11·9
	70	0·401	0·206	$KHSO_4$	0·513	1·7	10·5
	90	0·401	0·207	$KHSO_4$	0·605	1·6	9·0
	74	0·401	0·197	$KHSO_4$	1·00	1·7	7·2
	68	0·403	0·204	$NO{\cdot}HSO_4$	0·191	1·8	14·6
	50	0·403	0·173	$NO{\cdot}HSO_4$	0·20	(2·0)	14·3
	91	0·401	0·200	$NO{\cdot}HSO_4$	0·215	1·7	14·2
	92	0·401	0·209	$NO{\cdot}HSO_4$	0·333	1·8	11·6
	69	0·401	0·202	$NO{\cdot}HSO_4$	0·377	1·7	10·8

Discussion of Results.

We take the nitrating agent to be the NO_2^+ ion in all sulphuric acid media—from oleum to the equimolecular mixture of sulphuric acid and water, in which the NO_2^+ concentration falls virtually to zero (Bennett, Brand, and Williams, *loc. cit.*) and the nitration of DNT ceases (Table II, Fig. 3). In sulphuric acid–water media, the concentration of NO_2^+ ion is governed by the equilibria (4) and (5). The vapour pressure of water over sulphuric acid–water mixtures

$$NO_2{\cdot}OH + 2H_2SO_4 \rightleftharpoons NO_2^+ + OH_3^+ + 2HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad (4)$$

$$H_2O + H_2SO_4 \rightleftharpoons OH_3^+ + HSO_4^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

is exceedingly small if the water content is less than 14·5 wt.% (Daudt, *Z. physikal. Chem.*, 1923, **106**, 255), which justifies the assumption that equilibrium (5) lies virtually completely to the right in all mixtures in which sulphuric acid is present in molecular excess over water. In the following it is assumed that water is always completely converted into oxonium and bisulphate ions.

It is assumed further that the completion of nitration requires, not only the attachment of the NO_2^+ ion to the nucleus, but also the removal of a proton from the nucleus by a specific proton-acceptor, so that both acidic and basic functions of the medium are involved. We suppose, therefore, that the rate of nitration is governed by the frequency of suitable collisions between a DNT molecule, a NO_2^+ ion, and a proton-acceptor molecule. In sulphuric acid–water media, the most efficient proton-acceptor is probably the bisulphate ion; but this cannot be the sole available proton-acceptor, because the nitration velocity coefficient in 100% sulphuric acid has a value almost one-third as great as the maximum value in 92% sulphuric acid. The most probable additional proton-acceptor is the sulphuric acid molecule. That this molecule can accept protons is proved by its self-ionisation (Hantzsch, *Ber.*, 1925, **58**, 941; Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1900); and a possible mechanism for its action in nitration might be:

$$H^+ + H_2SO_4 \longrightarrow H_3SO_4^+$$

$$H_3SO_4^+ + HSO_4^- \rightleftharpoons 2H_2SO_4$$

The chemical equations for the nitration of DNT are (6) and (7):

$$DNT + NO_2^+ + HSO_4^- \longrightarrow TNT + H_2SO_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

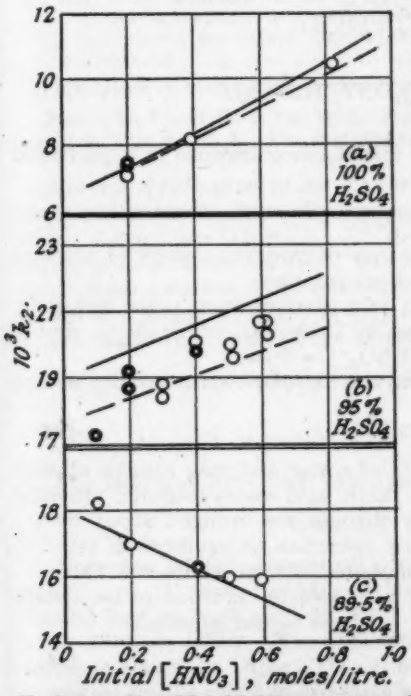
$$DNT + NO_2^+ + H_2SO_4 \longrightarrow TNT + H_3SO_4^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

The equation for the rate of nitration takes the form

$$d[TNT]/dt = k[DNT][NO_2^+][HSO_4^-] + k'[DNT][NO_2^+][H_2SO_4] \quad . \quad . \quad . \quad (8)$$

in which the constants k and k' are *independent of medium.*

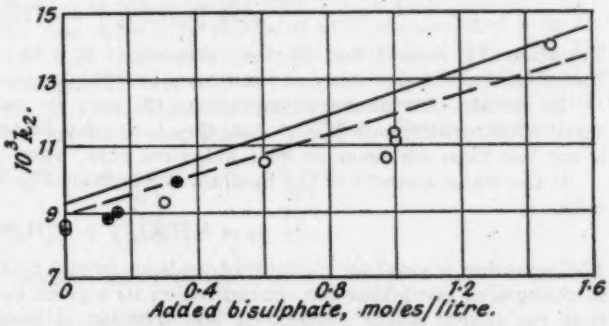
Fig. 4.



Variation of k_2 with initial concentration of nitric acid. Lines calculated, points experimental.

Full lines: $10^3 k = 3{\cdot}3$.
Broken lines: $10^3 k = 3{\cdot}0$.

Fig. 5.



Acceleration of nitration by added bisulphate in 99·2% H_2SO_4.
Open circles $KHSO_4$; crossed circles $NO{\cdot}HSO_4$.
Upper and lower lines calculated for $10^3k = 3{\cdot}3$ and 3·0.

Equation (8) may be transformed as follows, in order to express the nitration rate in terms of the measurable total concentration of nitric acid. Let $[HNO_3]$ represent the concentration of total nitric acid (all forms) in moles/litre, and let the molar concentrations of other species at equilibrium be $[NO_2{\cdot}OH]$ for undissociated nitric acid, $[H_2SO_4]$ for *free* (undissociated) molecular sulphuric acid, and $[NO_2^+]$, $[OH_3^+]$, $[HSO_4^-]$ for the ions. Then the " concentration " equilibrium constant of (4) is

$$K_c = \frac{[NO_2^+][OH_3^+]}{[NO_2{\cdot}OH]} \cdot \left\{\frac{[HSO_4^-]}{[H_2SO_4]}\right\}^2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

and since $[HNO_3] = [NO_2^+] + [NO_2{\cdot}OH]$, the fraction of nitric acid present as NO_2^+ ion given by

$$Q = \frac{[NO_2^+]}{[HNO_3]} = \frac{1}{1 + \frac{[OH_3^+]}{K}\frac{[HSO_4^-]^2}{[H_2SO_4]^2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

and equation (8) may be written in the form

$$d[TNT]/dt = \{k[HSO_4^-] + k'[H_2SO_4]\}[DNT][HNO_3]Q. \quad . \quad . \quad . \quad (11)$$

in which Q is determined by equation (10).

Experimentally, equation (1) holds for a fixed set of initial concentrations in a particular medium. By combination with equation (11),

$$k_2 = \{k[HSO_4^-] + k'[H_2SO_4]\}Q \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

Equation (12) should describe the variation of k_2 with change of medium, change of reactant concentration, or any other circumstance except change of temperature.

In certain circumstances, equation (12) may be put in a simpler form. For relatively small concentrations of HSO_4^- ion, $Q \sim 1$, as may be seen in Table VII, which shows that Q is not less than 0·97 even in 95% sulphuric acid, when $[HSO_4^-] = 5{\cdot}2$M.

If the water content of the medium is less than 5%, we can therefore write without serious error

$$k_2 = k[HSO_4^-] + k'[H_2SO_4] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

This equation is valid for changes of medium from 0 to 5% of water and may also be applied to changes of bisulphate ion concentration in a given sulphuric acid–water medium, provided that the (fixed) water content be less than 5%. Such changes are brought about by (*a*) variation of initial nitric acid concentration, through the operation of equilibrium (4); (*b*) addition of bisulphate ion as potassium or nitrosyl bisulphate (nitrous acid)—see Table V. Variation (*b*) leaves $[H_2SO_4]$ unaltered, so the change of k_2 caused by addition of bisulphate ion in a medium with less than 5% water content should be given by the equation

$$k_2 = k[HSO_4^-] + \text{const.} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The Constants of Equation (11).—These constants must be influenced by kinetic salt effects. However, since the salt effects (discussed further on p. 486) cannot be calculated quantitatively for the prodigious ionic strengths involved (*e.g.*, about 10 in 90% sulphuric acid), and since they cannot be predicted, with certainty, even qualitatively, the only course is to test the form of equation (11) by evaluating its constants provisionally, disregarding salt effects. This may be done, for k and k', by applying equations (13) and (14) to the experimental results for the variation of k_2 (equation 1) with medium, added bisulphate concentration, and initial nitric acid concentration, in solvents containing not more than 5% of water. The values for k and k' are shown in Table VI together with that of a third coefficient k'' concerned with the reaction in oleum, discussed below (p. 487). The agreement in the results derived from independent experimental sources is not unsatisfactory. A further independent estimate for k (and K_c) may be obtained by neglecting the term $k'[H_2SO_4]$ in equation (12), which is much smaller than the term $k[HSO_4^-]$ in all but the least aqueous media (those in which the molar ratio $H_2O/H_2SO_4 < 0{\cdot}2$, see Table VII). This is equivalent to supposing that the bisulphate ion is the only effective proton-acceptor in the more aqueous media. Two sets of experimental results (Table II) are inserted in the modified form of equation (12), Q being given by equation (10), and simultaneous equations are solved for k and K_c. The results, together with others calculated on the same assumption, are given in Table VI as " 1st Approx.". The simplifying assumption is seriously inaccurate for the results in this column derived from data II and III.

TABLE VI.

Evaluation of the constants k, k′, *and* k″.

Experimental source.	10^3k.	$10^3k'$.	$10^3k''$.	1st Approx. 10^3k.
I. Accelerating influence of $KHSO_4$ and $NO{\cdot}HSO_4$ in 99·3% H_2SO_4 (Table V, Fig. 5)	3·3	—	—	3·3
II. Accelerating influence of increased initial concentration of HNO_3:				
(*a*) in 100% H_2SO_4	3·1	0·37	—	2·5
(*b*) in 95% H_2SO_4 (Table III, Fig. 4)	3·0	0·33	—	2·3
III. Accelerating influence of water on acid side of optimum medium composition (Table II, Fig. 3)	3·0	0·38	—	2·7
IV. Retarding influence of water on water side of optimum medium composition (Table II, Fig. 3)	—	—	—	3·5
(calculated for media with $H_2O/H_2SO_4 = 0{\cdot}55$ and 0·70)	—	—	—	$K_c = 33$
V. Variation of oleum composition (Table VIII)	—	0·37	0·56	—

Note.—In I and II, k has been calculated from the experimental points, and not from the lines drawn in Figs. 4 and 5. The meaning of the lines is explained later.

General Application of the Theoretical Equation.—In order to apply equation (12) to the whole of the results, its constants are derived in the following way: (1) A representative value of k is taken from Table VI. (2) Using this value of k, the value of k' is calculated from the experimental results for 100% sulphuric acid medium by means of equation (13). (3) The equilibrium constant K_c of the nitric acid equilibrium (4) has been evaluated by inserting the values of k and k' in equation (12) with (10) and then applying the equation to experimental points on the water side of the optimum medium composition, with the following results:

Medium, H_2O/H_2SO_4.	k_2, exptl.	K_c, calc.
0·80	6·1	35·8
0·70	13·0	33·7
0·55	21·0	31·4

The following have been taken as representative values:

$$k = 3{\cdot}3 \times 10^{-3};\ k' = 0{\cdot}37 \times 10^{-3};\ K_c = 33{\cdot}6.$$

For some preliminary calculations we derived a rough value of 30—42 for the constant of equilibrium (4) from Chédin's estimates (*Ann. Chim.*, 1937, **8**, 243) of the intensities of the Raman line $\Delta\nu$ 1400 cm.$^{-1}$ (cf. Part I, *loc. cit.*) in sulphuric acid–nitric acid–water mixtures.

I. *Medium Effect.*—The application of equation (12) to the calculation of k_2 in different media is shown in Table VII. The required concentrations of the various molecular species furnished by the medium are calculated on the assumption that water is, in all circumstances, *completely* converted into oxonium and bisulphate ions. The figures in Table VII have also the limitation that they hold only for the conditions DNT = 0·4M and HNO_3 = 0·2M. Allowance is made for the bisulphate-ion concentration contributed by the nitric acid (equilibrium 4). To compute correctly the amount of sulphuric acid furnished by the medium, allowance must also be made for the volume taken up by DNT (Table XII) and a further small correction is applied for "volume" occupied by nitric acid. This last correction becomes appreciable when larger concentrations of nitric acid are involved (see Experimental section).

From the value of Q as a function of medium composition in Table VII it may be appreciated that the rise in k_2 with increasing water content in media on the acid side of the optimum is due to the increased concentration of HSO_4^- (acting as proton-acceptor) by the operation of equation (5), because the extent of ionisation of nitric acid falls relatively slowly in this region; whilst the fall in k_2 in media on the water side of the optimum is caused by the rapid fall in the extent of nitronium-ion formation as governed by equation (4) when H_2O/H_2SO_4 exceeds 0·5. For this reason, the constant k is best evaluated from data falling on the "acid limb" and K_c from data on the "water limb".

The columns headed "$3{\cdot}3[HSO_4^-]$" and "$0{\cdot}37[H_2SO_4]$" in Table VII represent the relative contributions to nitration speed due to proton-acceptance by bisulphate ions and sulphuric acid molecules respectively. Their sum, multiplied by Q, gives the final value of k_2, calc. The calculated curve for the variation of nitration velocity coefficient with medium com-

TABLE VII.

Calculation of influence of medium upon nitration rate.

Medium. H_2O / H_2SO_4	Medium. H_2SO_4, Wt. %	$[OH_3^+]$, M.	$[HSO_4^-]$, M.	$[H_2SO_4]$, M.	Q, $[NO_2^+]/[HNO_3]$	$3{\cdot}3[HSO_4^-]$.	$0{\cdot}37[H_2SO_4]$.	10^3k_2, calc..
0	100	0·2	0·4	16·42	1	1·32	6·08	7·40
0·075	98·70	1·44	1·64	15·00	1	5·41	5·55	10·96
0·1	98·20	1·86	2·06	14·50	0·999	6·80	5·36	12·15
0·128	97·70	2·32	2·52	13·96	0·998	8·32	5·17	13·46
0·2	96·46	3·45	3·65	12·61	0·992	12·05	4·66	16·57
0·3	94·78	4·98	5·18	10·76	0·967	17·09	3·98	20·37
0·4	93·16	6·43	6·62	9·02	0·907	21·83	3·34	22·82
0·45	92·37	7·14	7·31	8·18	0·855	24·12	3·03	23·21
0·475	91·98	7·48	7·65	7·74	0·821	25·24	2·87	23·09
0·55	90·82	8·47	8·61	6·53	0·695	28·40	2·42	21·43
0·65	89·30	9·77	9·87	4·95	0·464	32·58	1·83	15·96
0·7	88·61	10·30	10·34	4·32	0·363	34·11	1·60	12·96
0·8	87·19	11·50	11·53	2·81	0·147	38·03	1·04	5·76

position is shown as the full line in Fig. 3, where it is compared with the experimental results from Table II.

The calculated line lies above the experimental points in the most concentrated sulphuric acid media and below them in the region of the optimum medium. Table VI shows that results in concentrated sulphuric acid media are represented better by the value $10^3k = 3{\cdot}0$ than by the value 3·3, used in Table VII and Fig. 3 as giving the best representation of the results as a whole. An alternative curve calculated with the constants $k = 3{\cdot}0 \times 10^{-3}$, $k' = 0{\cdot}38 \times 10^{-3}$, $K_c = 34{\cdot}6$, is in better accord with experiment in concentrated sulphuric acid media, but lies still further below the observed maximum velocity coefficients. It is possible that $10^3k = 3{\cdot}0$ is the better value (see discussion below on kinetic salt effects).

In Fig. 4 (*a*) and (*b*) and in Fig. 5, calculated lines are shown for both values of k. Fig. 5 gives a calculation from equation (14) for the influence of added bisulphate in 99% sulphuric acid, compared with the experimental results of Table V.

The broken curve in Fig. 3 is derived from the " 1st Approx." constants $k = 3{\cdot}5 \times 10^{-3}$, $K_c = 33$, $k' = 0$. This curve must fail on the acid side of the optimum because it is drawn on the assumption that bisulphate ion is the sole proton-acceptor, so that k_2 must fall almost to zero in 100% sulphuric acid. It is included for its significance in showing that from two points on the water side of the optimum (cf. Table VI) constants may be calculated which predict a maximum rate of nitration in a medium of just about the composition actually observed.

Kinetic Salt Effects.—The numerical values deduced for the constants of equation (11) —and of equation (16)—should be regarded as partly empirical. The variation of the experimental velocity coefficient k_2 with medium and with nitric acid concentration has been expressed in terms of invariant coefficients k and k'. But these must be subject to primary kinetic salt effects, which have been disregarded; so that k and k', as calculated above, should not be strictly independent of medium. Since k and k' are evaluated from experiments at relatively low ionic strength (Table VI) and since, also, salt effects must be unusually small in sulphuric acid as solvent (Hammett and Deyrup, *loc. cit.*) the values employed are perhaps not far removed from those which would be appropriate to " zero " ionic strength. The salt effects acting on k and k' in relatively aqueous media cannot be estimated theoretically, even qualitatively, without knowing how the activity coefficients of the various ions and neutral molecules involved in reactions (4) and (5) change at very high ionic strengths. There are experimental indications that k may rise with increasing ionic strength, which may help, if substantiated, to explain why the calculated curve in Fig. 3 lies below the experimental results in the region of the optimum medium.

The concentration of NO_2^+ ion will also be influenced by secondary salt effects, not taken into account by equation (9); but these will only be considerable in media on the aqueous side of the optimum composition, for it is only here that nitric acid behaves as a weak electrolyte. The equilibrium constant K_c is evaluated from experiments in these more aqueous media and should therefore automatically contain some allowance for secondary salt effects.

A further factor which has been left out of account is that collision frequencies of DNT molecules or NO_2^+ ions with sulphuric acid molecules or bisulphate ions may be affected by changes of viscosity in different media.

II. *Concentration Effects.*—Increase of initial nitric acid concentration means that an

increased concentration of bisulphate ions is present throughout the nitration. If the medium is one in which increased bisulphate concentration accelerates nitration, then k_2 will rise with increased nitric acid concentration. If bisulphate ion has the opposite effect, then k_2 will fall. In either event, the extent of the variation of k_2 should be given by equation (12). In Fig. 4 the full lines are calculated from equation (12) for three different media, allowance being made for decrease in the amount of sulphuric acid present as the amount of nitric acid is increased. The experimental results are also shown in the diagrams. For 95% sulphuric acid medium with $k = 3{\cdot}3 \times 10^{-3}$ the equation reproduces the gradient of k_2 but gives absolute values which are too high throughout. The broken lines are for $k = 3{\cdot}0 \times 10^{-3}$.

Changes of concentration *during* the nitration reaction do not bring about any appreciable drift of k_2, because the bisulphate ions originally derived from nitric acid are largely replaced by new bisulphate ions derived from the products, nitrous acid and water.

The Influence of Initial DNT *Concentration.*—Equation (12) does not predict any variation of k_2 with initial DNT concentration. In fact, such a variation is observed (Table IV). It is not large, but it is of the same order of magnitude as the variation of k_2 with initial nitric acid concentration; and, like the latter, it is of opposite sign in media on either side of the optimum. For 0·2M initial nitric acid concentration, the variation of k_2 with initial DNT concentration is given empirically by the equations

$$\text{In 100\% } H_2SO_4 \text{ medium: } 10^3k_2 = 5{\cdot}5 + 5{\cdot}1[\text{DNT}]_{t=0}$$

$$\text{In 89·5\% } H_2SO_4 \text{ medium: } 10^3k_2 = 20{\cdot}6 - 7{\cdot}9[\text{DNT}]_{t=0}$$

No explanation can be given for this variation at present; but we believe it to be connected, in some way, with the oxidation reaction, because this kind of variation is not observed in the nitrations of *p*-chloronitrobenzene and nitrobenzene which are otherwise closely analogous to that of DNT. A qualitatively attractive explanation is that additional bisulphate-ion concentration is formed by ionisation of the fragments X_f of p. 477; but the concentrations of X_f are easily calculated to be insufficient to account for the magnitude of the effect. Change in the amount of sulphuric acid in the reaction mixture with variation of initial DNT concentration (Table XII) is also inadequate as an explanation of the effect. Further experiments are needed.

Nitration in Oleum Media.—Results in oleum media are given in Tables VIII and IX.

TABLE VIII.

Nitrations in oleum media (Temp. 89·9°).

Medium.							
Wt. % free SO_3.	Acid No.	$\frac{SO_3}{H_2SO_4}$.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	$\frac{[TNT]}{[HNO_3]}$.	10^3k_2.
7·8	23	0·104	173	0·3998	0·2003	1·8	5·8
			174	0·4002	0·2003	1·6	5·4
			176	0·3994	0·8000	1·7	7·9
			175	0·7975	0·2034	2·0	8·4
11·7	26	0·162	177	0·3998	0·1998	1·7	5·5
			178	0·4009	0·1986	1·8	5·3
16·6	25	0·244	171	0·4004	0·2052	2·2	4·7
			172	0·4000	0·2024	2·4	5·1
29·1	27	0·503	179	0·4006	0·1960	(1·3)	(2·8)
			180	0·4001	0·2053	(2·3)	(3·1)

The velocity coefficients in 29·1% oleum are not accurate, owing to analytical difficulties; but the reaction curves showed unmistakably that nitration was slower in 29·1% oleum than in 16·6% oleum. Thus, the rate of nitration is less in oleum media than in 100% sulphuric acid; and decreases with rising proportion of sulphur trioxide in the oleum. This behaviour may be ascribed to the decreasing opportunities for proton-removal in oleum media. For the bipyrosulphate ion, being more weakly basic, will accept a proton less readily than the bisulphate ion; and the concentration of sulphuric acid molecules falls as the sulphur trioxide content of the oleum increases. Pyrosulphuric acid is a stronger acid than sulphuric acid.

Extension of Theory to Oleum Media.—In oleum media the principal proton-acceptors are probably the sulphuric acid molecule and the bipyrosulphate ion; nitration will take place according to equations (7) and (15):

$$\text{DNT} + NO_2^+ + HS_2O_7^- \longrightarrow \text{TNT} + H_2S_2O_7 \quad . \quad . \quad . \quad . \quad (15)$$

The rate of nitration is given by equation (16) :

$$d[TNT]/dt = k'[DNT][NO_2^+][H_2SO_4] + k''[DNT][NO_2^+][HS_2O_7^-] \quad . \quad . \quad . \quad (16)$$

which may be put in the form

$$d[TNT]/dt = \{k'[H_2SO_4] + k''[HS_2O_7^-]\}[DNT][HNO_3]Q$$

where $Q = [NO_2^+]/[HNO_3] = 1$ in oleum.

Hence

$$k_2 = k'[H_2SO_4] + k''[HS_2O_7^-] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

To draw up a concentration table for oleum media, analogous to Table VII, it is necessary to make assumptions about the fraction of pyrosulphuric acid which exists as $HS_2O_7^-$ ion in sulphuric acid solution. The identity of the cations existing in such a solution is not certain. We have made the calculation by postulating the equilibrium :

$$H_2SO_4 + H_2S_2O_7 \rightleftharpoons H_3SO_4^+ + HS_2O_7^- \quad . \quad . \quad . \quad . \quad . \quad (18)$$

for the relatively strong oleums in question, and by taking a value of 1 for its equilibrium constant. This figure gives results which are consistent with chemical evidence (Part III, Brand, *J.*, 1946, 880) about the relative strengths of sulphuric and pyrosulphuric acids. It being assumed that nitric acid, in these relatively strong oleums, is completely converted into NO_2^+ ion according to equation (19), the concentrations $[HS_2O_7^-]$ and $[H_2SO_4]$ may be calculated

$$NO_2{\cdot}OH + 2H_2S_2O_7 = NO_2^+ + HS_2O_7^- + 2H_2SO_4 \quad . \quad . \quad . \quad . \quad (19)$$

for different oleums and combined with the experimental values of k_2 from Table VIII to determine the constants of equation (16).

TABLE IX.

Variation of temperature.

Temp.	Medium. Wt. % H_2SO_4.	Acid No.	H_2O/H_2SO_4.	Expt. No.	Initial concn. of DNT, M.	Initial concn. of HNO_3, M.	$[TNT]/[HNO_3]$.	10^3k_2.
80°	100	31	0	209	0·3959	0·1969	1·6	2·84
80	,,	31	,,	210	0·3966	0·2003	1·8	2·78
70	,,	31	,,	211	0·3970	0·2007	3·1	1·13
70	,,	31	,,	212	0·3967	0·2011	2·7	1·13
120	95·0	39	0·283	239	0·4004	0·2011	0·95	251
120	,,	39	,,	240	0·4000	0·2006	0·90	221
110	,,	39	,,	236	0·4000	0·1987	0·94	104
110	,,	39	,,	237	0·3995	0·1994	1·2	104
110	,,	39	,,	238	0·3999	0·2005	1·05	106
100	,,	39	,,	234	0·3994	0·2023	1·1	43·7
100	,,	39	,,	235	0·3994	0·1967	1·1	41·1
80	,,	29	0·287	185	0·4000	0·2004	1·9	7·5
80	,,	29	,,	186	0·3998	0·1957	1·8	8·0
80	,,	29	,,	187	0·4001	0·2002	1·9	7·6
70	,,	29	,,	188	0·4005	0·2013	2·1	2·90
70	,,	29	,,	189	0·4000	0·1998	2·3	2·92
70	,,	29	,,	190	0·6001	0·2013	2·2	3·36
60	,,	29	,,	194	0·3999	0·2011	2·3	1·00
60	,,	29	,,	195	0·4006	0·2041	2·7	1·02
110	89·5	40	0·636	247—250	0·4004	0·2006	1·2	84
100	,,	40	,,	244	0·4004	0·2000	1·4	(35·0)
100	,,	40	,,	245	0·3999	0·2002	1·4	37·3
100	,,	40	,,	246	0·4008	0·1991	1·4	36·9
70	,,	30	0·638	198	0·3987	0·2004	2·5	2·65
70	,,	30	,,	199	0·4004	0·2008	2·4	2·54
80	87·6	43	0·770	289	0·3999	0·2003	1·6	2·9
80	,,	43	,,	291	0·3993	0·2001	1·8	2·6
	Wt. % SO_3.	Acid No.	SO_3/H_2SO_4.					
80	7·8	23	0·104	192	0·4000	0·1934	1·4	2·06
80	,,	,,	,,	193	0·3999	0·1995	1·8	2·33
70	,,	,,	,,	196	0·3998	0·1995	1·8	0·76
70	,,	,,	,,	197	0·4000	0·2007	2·5	0·84

Solving simultaneous equations for each of the oleum pairs 7·8—16·6% SO_3 and 11·7—29·1% SO_3, we find $10^3k' = 0·35$ and 0·39, to be compared with the value 0·37 deduced for aqueous sulphuric acid media (Table VI). Inserting the value 0·37 in equation (16), we find for the four different oleum media: $10^3k'' = 0·47$, 0·60, 0·60, 0·55. A theoretical curve to represent the variation of k_2 in different oleum media has been drawn from equation (16) with $k' = 0·37 \times 10^{-3}$ and $k'' = 0·56 \times 10^{-3}$. The curve is shown in the right-hand portion of Fig. 3.

General Equation.—The foregoing argument thus leads to the general equation

$$d[TNT]/dt = \{k[HSO_4^-] + k'[H_2SO_4] + k''[HS_2O_7^-]\}[DNT][HNO_3]Q$$

which reproduces the velocity observations over the entire range of media studied.

Influence of Temperature.—The variation of k_2 with temperature for several media may be een from Table IX, together with results for 90° from previous tables.

For a given medium, log k_2 falls on a straight line when plotted against $1/T$. Since the rate of nitration is given by the sum of two terms—equations (11) or (16)—deviations from the Arrhenius equation might have been anticipated. However, the temperature range is not great, and since the differences between k, k', and k'' are due only to differences of basic strength between HSO_4^-, H_2SO_4, and $HS_2O_7^-$, their temperature variations may well be similar. From the results for different media, the constants of equation (11) may be calculated roughly for different temperatures. The temperature variation of k_2 is due mainly to changes in the coefficients k and k'. The constants of the Arrhenius equation for different media are shown in Table X.

TABLE X.*

Contants of the equation $k_2 = Ae^{-E/RT}$.

Medium.	E (kg.-cals.).	$A \times 10^{-10}$.
7·8% SO_3	24·18	3·3
100% H_2SO_4	23·35	1·4
95·0% H_2SO_4	23·54	4·7
89·5% H_2SO_4	22·58	10·5
87·6% H_2SO_4	22·32	0·71

* In this table, k_2 is calculated in *seconds*$^{-1}$. The significance of the temperature variation of nitration speed will be considered in a later paper, when the results for DNT can be combined with those for other compounds nitrated at much lower temperatures.

EXPERIMENTAL.

Materials.—2 : 4-Dinitrotoluene was prepared by the nitration of *p*-nitrotoluene and recrystallised from alcohol until its setting point was constant. The setting point was taken on 10—15 g. of molten material, allowed to cool slowly in a Thermos jacket, previously warmed to 70°. Pure nitric acid was obtained by distilling a mixture of 70% nitric acid and 98% sulphuric acid, in a volume ratio of approximately 2 : 3, at about 15 mm. pressure. Alkali titration of the distillate gave its purity as 99·97% (mean). It was normally dissolved without delay in sulphuric acid to give 0·0008 mole/g. of nitric acid. Salts: "AnalaR" Potassium sulphate, potassium hydrogen sulphate, and potassium nitrate were employed, dried in the oven before use.

Nitration Media.—Solutions for a nitration experiment were made up in two vessels, one containing a solution of DNT in sulphuric acid medium, the other a solution of nitric acid in medium having the same molecular ratio H_2O/H_2SO_4. The reaction was started by mixing these two solutions. For each medium, therefore, two stock solutions were made up, one being the pure medium, the other a solution of nitric acid in this medium. Both solutions were analysed before use.

(1) Sulphuric acid–water media were made up by weight from 98% sulphuric acid. The nitric acid solution was obtained by adding pure nitric acid to the medium already prepared. All solutions were analysed at least in duplicate. Analyses were made on weighed samples, suitably diluted; *e.g.*,

Medium NM/20. By alkali titration: 95·0$_2$, 94·8$_7$, 95·2$_5$%; mol. ratio $H_2O/H_2SO_4 = 0·284$.
Corresponding nitric acid solution.
Total acid (against alkali): 0·00191$_9$, 0·00192$_2$ equiv./g.
Nitric acid (by ferrous sulphate): 0·000842$_9$, 0·000842$_7$ mole/g.
Hence, mol. ratio $H_2O/H_2SO_4 = 0·285$.

The strengths of sulphuric acid–water media were sometimes checked by density measurements, a 2-c.c. pyknometer being used at 25°. The method is only satisfactory for acids containing less than 95% sulphuric acid.

(2) 100% Sulphuric acid medium was made up by adjusting a weak oleum to maximum freezing point (Hantzsch, 1907, *loc. cit.*). Alkali titration gave its strength as 99·95% H_2SO_4 (mean). To make the corresponding nitric acid solution, pure nitric acid was added to 100% sulphuric acid. Analysis by alkali and ferrous sulphate gave a water content of −0·003%.

(3) *Oleum media.* Sulphur trioxide was distilled (*ca.* 45°) from commercial oleum (*ca.* 20% free SO_3) into sulphuric acid, and then redistilled into a second sample of sulphuric acid to form a stock solution (containing up to 40% free SO_3). The stock distillate was diluted with sulphuric acid to

give the required medium composition and analysed for free sulphur trioxide by titrating with water (Brand, *J.*, 1946, 585). A solution of nitric acid in oleum was also made up, to have the same ratio SO_3/H_2SO_4, by adding pure nitric acid to the oleum medium prepared as above. Nitric acid in this solution was estimated by ferrous sulphate titration. The SO_3/H_2SO_4 ratio in the nitric acid solution was checked by water titration, use being made of the fact that one mole of nitric acid, dissolved in oleum, prevents the fuming of 1·5 mole of sulphur trioxide (Brand, Part III, *loc. cit.*).

Example: Water titration of an oleum medium gave its sulphur trioxide content as 29·1% (mean) and its molar ratio SO_3/H_2SO_4 as 0·503. The corresponding nitric acid solution contained 0·000886$_3$ mole/g. HNO_3. By water titration, apparent SO_3 content = 0·002110 mole/g. SO_3 equivalent of HNO_3 = 0·001329 mole/g. Therefore, real SO_3 content = 0·003439 mole/g.; and molar ratio SO_3/H_2SO_4 = 0·504, in agreement with the medium before adding nitric acid.

100% Sulphuric acid and oleum media were stored in a special apparatus, from which they could be drawn into the reaction flasks without coming into contact with moist air.

The compositions of all types of media were frequently tested by re-analysis.

Velocity Measurements.—Temperature was controlled to within ± 0·075° by an electrically operated water thermostat. The water was covered by a layer of paraffin oil. The thermometer was calibrated against the transition temperature of strontium bromide (88·62°; Richards and Yngve, *J. Amer. Chem. Soc.*, 1918, **40**, 89). Most of the reactions took place at 89·9°. At higher temperatures a glycerol thermostat was used.

Start of reaction. Two solutions, one of DNT and one of nitric acid, both in the same medium, were made up to 50 c.c. at thermostat temperature in Pyrex graduated flasks. The reaction vessel was a stoppered glass bottle, large enough to allow rapid mixing of the reactants by shaking. The two reactant solutions were poured successively into the bottle and the latter shaken. Draining errors for equal volumes poured from equal sized vessels are negligible. The starting time of the reaction was taken as 30 secs. after the beginning of pouring the second (nitric acid) solution into the reaction vessel.

In the later experiments, a special apparatus was used to give quick mixing and to eliminate temperature disturbances at the start of a reaction. The whole apparatus was immersed in the thermostat; and the two solutions were admitted simultaneously into the reaction bulb through ground necks, fitted with stoppers.

Extraction of samples. The samples for analysis (5 c.c. for HNO_3; 2 c.c. for HNO_3) were withdrawn in pre-heated pipettes, drained for 15 secs. The pipettes were calibrated for delivery of sulphuric acid medium, levelled to the pipette mark at the reaction temperature. Two methods of calibration were used: (*a*) direct weighing of the sulphuric acid medium delivered, coupled with a measurement of the density of the medium at 90°; (*b*) a more exact reproduction of the conditions prevailing when withdrawing samples from a reaction in progress: a solution of nitric acid of known concentration was made up in sulphuric acid medium at reaction temperature. Samples were extracted and analysed for nitric acid, thus providing a calibration factor for the pipette. For example, at 90°: calibrated by method (*a*), a 2-c.c. and a 5-c.c. pipette delivered 1·996 ± 0·0014 and 5·01 ± 0·0053 c.c. respectively (mean of five determinations for each); calibrated by method (*b*), another pipette delivered 2·013 ± 0·003 c.c. (five determinations).

Analytical Methods.—1. *For nitrous acid.* Considerable work was done upon methods of estimating nitrous acid. Satisfactory results for the conditions of the nitration experiments were obtained by running 2-c.c. samples either into standard chloramine-T solution, buffered by sodium acetate, or into standard ceric sulphate solution, residual reagent being determined in both methods with potassium iodide and sodium thiosulphate. The chloramine-T method is not accurate for reactions in oleum media; but in other media results from the two methods are concordant.

2. *For nitric acid.* The 5-c.c. sample was run into about 20 c.c. of concentrated sulphuric acid, cooled in ice, and titrated against standard ferrous sulphate solution by the electrometric method of Treadwell and Vontobel (*Helv. Chim. Acta*, 1937, **20**, 573). The ferrous sulphate is dissolved in 30% sulphuric acid.

The proportion of sulphuric acid present must not fall below 75% at the end of the titration. A ferrous sulphate solution gave values 0·4550, 0·4548, and 0·4552 N., when standardised, respectively, against standard potassium nitrate in concentrated sulphuric acid, against aqueous standard potassium nitrate, and against aqueous standard nitric acid, the last two being run into concentrated sulphuric acid for titration. Ferrous sulphate concentrations of 0·1, 0·32, and 0·64 N. were ordinarily used, according to the initial concentration of nitric acid in the reaction mixture. The presence of DNT did not affect the sharpness of the end-point.

Calculation of Results.—The quantities measured during the course of nitration are (*a*) the decrement of nitric acid concentration, and (*b*) the increment of nitrous acid concentration, both at known times. The calculation of the amount of nitric acid consumed in nitration as the difference between the total amount consumed and the amount of nitrous acid formed involves the assumption that no nitric acid is consumed in any other way than in the formation of TNT and nitrous acid. No evidence against this assumption has been obtained except in the most aqueous medium investigated, 87·4% sulphuric acid. Some evolution of nitrous fumes was observed during nitration in this medium, especially in the presence of added nitrosyl bisulphate. In more concentrated sulphuric acid media, fuming is absent, probably owing to the relatively high degree of ionisation of nitric acid to nitronium ion. Equating the amount of nitric acid consumed in nitration (increment in TNT concentration) to the amount of DNT consumed involves the further assumption that the amount of DNT consumed in oxidation is small compared with that consumed in nitration. This assumption has been tested experimentally.

Composition of Nitration Product: Density Method.—In order to determine how accurately the increase in TNT concentration is measured by the observed changes in nitric and nitrous acid concentrations, the composition of the nitration product has been found, in a number of reactions, by an independent method. A sample of reaction mixture (*ca.* 80 c.c.) is drowned in ice-cold water at a

known time. The precipitated solid mixture of DNT and TNT is filtered off and freed from acid by repeated washing of the molten material with water. The product is finally dried for not more than 3 hours in the steam-oven, and its density is taken in a 2-c.c. pyknometer at 90°. Its TNT content is deduced from a curve relating the densities of DNT–TNT mixtures at 90° to their composition. One of many checks on the drowning and washing procedure gave the following results:

14·002 G. of a mixture of DNT and TNT, containing 50·3% of TNT, density at 90° 1·3783, was melted under 500 c.c. of water containing 34 g. of nitrating acid. The mixture was cooled and filtered, and the solid freed from acid in the usual way. Density of dried product: 1·3875, 1·3778; average 1·3782, corresponding to 50·2% TNT. The recovery of solid was 13·653 g., or 97·5%.

Results of density measurements are given in Table XI. The figures under " % of possible reaction " in this table refer to over-all consumption of whichever reactant is present in defect. Since nitric acid is used up to form both TNT and nitrous acid, DNT can only be considered to be in defect if the initial proportion of nitric acid to DNT is greater than about 1·7 : 1. Only then does " % of possible reaction " become identical with " % Conversion of DNT ". The last two columns of Table XI give comparative results for the extent of conversion of DNT into TNT in homogeneous nitration, as determined by acid analysis and by density. Agreement is satisfactory in Table XI (A), with DNT present in initial molecular excess over nitric acid. Deviations are not large even after more than 90% consumption of nitric acid (Expts. 152, 160). Under these conditions, therefore, it may be assumed that the amount of DNT consumed in oxidation is small and that losses of nitric acid are negligible.

The agreement is sometimes less satisfactory with equivalent initial proportions of DNT and nitric acid; and discrepancies become marked when nitric acid is present in excess [Table XI (B)], particularly when the extent of conversion of DNT exceeds 35%. (It appears, however, that the factor determining the occurrence of discrepancy is excess nitric acid, rather than mere extent of conversion—Expts. 150, 183.) In these circumstances, the conversion deduced from the density of the product is always greater than that found by acid analysis. A discrepancy in this direction could arise from loss of DNT in oxidation, but not from loss of nitric acid. (Loss of nitric acid would result in overestimate of TNT formation by acid analysis.)

Another possibility is that the nitration product, when isolated, contains some substance other than DNT and TNT, *i.e.*, some reaction product with density higher than that of DNT. However, extraction of nitration product with sodium hydrogen carbonate solution after its density had been determined gave a residue whose density was unchanged after being re-washed and dried (Expt. 181). Similar results were obtained with products from oleum media. The molecular ratio of TNT formed to nitrous acid formed (both estimated by acid analysis) appears to be much the same whether DNT or nitric acid is in excess (Tables III and IV).

TABLE XI.

Extent of nitration, estimated by density of product and by acid analysis (Temp. 89·9°).

Medium.	Expt. No.	Initial concn. DNT, M.	Initial concn. HNO_3, M.	% of possible reaction.	% Conversion of DNT. By density.	% Conversion of DNT. By acid analysis.
(A) With initial excess of DNT.						
Oleum:						
16·7% SO_3	171 *	0·400	0·205	38·2	12·5	12·8
7·8% "	173 *	0·400	0·200	47·3	14·5	14·0
Aq. sulphuric acid:						
96% H_2SO_4	43	0·385	0·207	66·2	20·9	20·9
95 "	146	0·401	0·204	73·6	22·5	22·0
95 "	152	0·401	0·206	96·9	30·2	28·6
95 "	185 †	0·400	0·200	72·6	23·4	22·8
95 "	189 ‡	0·400	0·200	44·1	14·4	14·8
89·5 "	160	0·401	0·101	92·8	13·4	14·4
89·5 "	154	0·398	0·199	66·5	21·4	21·0
89·5 "	155	0·598	0·201	74·2	15·8	16·2
89·5 "	158	0·802	0·199	80·0	11·9	12·5
(B) Without initial excess of DNT.						
99 "	4	0·302	0·315	56·1	32·7	33·1
96 "	39	0·321	0·311	49·7	29·2	29·8
95·7 "	150	0·398	0·614	22·0	23·8	22·3
95·7 "	183	0·400	0·604	22·0	21·5	20·4
95·7 "	181	0·400	0·607	59·0	60·1 §	53·5
95 "	148	0·401	0·606	60·0	63·2	55·0
95 "	144	0·401	0·595	60·9	62·3	53·8
95 "	153	0·401	0·603	60·7	60·8	52·4
89·5 "	156	0·250	0·200	73·3	38·4	35·5
89·5 "	159	0·401	0·400	54·0	36·7	34·5
89·5 "	161	0·400	0·594	48·5	49·9	48·5

* HNO_3 by ceric sulphate. † At 80°. ‡ At 70°.
§ After extraction by $NaHCO_3$, 60·2%.

Reproducibility of Results.—Data for a duplicate pair of experiments are shown in Fig. 1. Others may be found in the tables (*e.g.*, Tables VIII and IX). Concordance in the results from the chloramine-T and the ceric sulphate method for estimating nitrous acid is illustrated by Expts. 99, 100, and 101 of Table III. The agreement between results for identical concentrations in independently prepared but matched media may be judged from the tables, by comparing media having approximately the same composition but different "Acid No." (*e.g.*, in Table III, for 100% and 95·1% H_2SO_4; cf. also Fig. 3).

Amounts of Medium in Reaction Mixtures.—For theoretical reasons it is necessary to know, not only the molar concentrations of DNT and nitric acid, but also the molar concentrations of sulphuric acid and water present in all reaction mixtures. Since reaction mixtures are always made up to a definite *volume*, the weight of a given medium present varies for different concentrations of DNT and nitric acid. The correction for volume of DNT is considerable; that for nitric acid is smaller, but is noticeable for the higher nitric acid concentrations. It is not practicable to weigh the complete reaction mixtures, so experiments have been made to furnish corrections applicable for each reactant separately.

1. DNT *Correction.* Flasks of known volume, containing known weights of DNT, were filled to the mark at 90° with sulphuric acid medium and then weighed. The densities of DNT and medium at 90° are known, so the partial volumes of DNT and sulphuric acid medium may be calculated. The results in Table XII show, for two different sulphuric acid media, that the volumes of DNT and media

TABLE XII.

Additivity of volumes in DNT–*sulphuric acid mixtures at* 90°.

DNT, mole/l.	Wt. of DNT, g.	Wt. of acid, g.	Partial vol. of DNT, c.c.	Partial vol. of acid, c.c.	Sum of vols., c.c.	Vol. o flask, c.c.
(*a*) For 95·0% sulphuric acid, $d^{90°} = 1·768$ g./c.c.						
0·0998	0·910	87·304	0·7	49·4	50·1	50·1
0·2008	1·820	85·759	1·4	48·5	49·9	49·9
0·3993	3·651	83·647	2·8	47·3	50·1	50·1
0·602	5·463	80·893	4·2	45·75	49·95	49·9
0·802	7·312	78·734	5·6	44·5	50·1	50·1
1·198	10·924	73·490	8·3	41·6	49·9	49·9
(*b*) For 89·5% sulphuric acid, $d^{90°} = 1·743$ g./c.c.						
0·1002	0·910	85·672	0·7	49·2	49·9	49·9
0·4000	3·647	82·485	2·8	47·3	50·1	50·1
0·8013	7·277	77·179	5·6	44·3	49·9	49·9
For DNT, $d^{90°} = 1·310$ g./c.c.						

are strictly additive. Thus, the volume of medium (and hence the weight) in a reaction mixture can be calculated for any initial amount of DNT. Volume corrections for other temperatures were estimated, assuming additivity, by applying the interpolation formula given by Schiff (*Annalen*, 1884, **223**, 247) for the density of DNT.

2. *Nitric acid correction.* Although densities are available for nitrating acids, the corrections to be applied were estimated directly by determining the weights of sulphuric acid–water media in 100 c.c. of mixture at 90° for various nitric acid concentrations and for various proportions of sulphuric acid and water. The corrections were less than 1% for 0·2M-HNO_3, rising to about 2% and 3% respectively for 0·8M-HNO_3 in 99% and 89·5% sulphuric acid media.

Our studies of nitration were begun in 1940 in the laboratory of Professors W. E. Garner, F.R.S., and E. L. Hirst, F.R.S., to whom our cordial thanks are due.

We wish to thank the Chief Scientific Officer of the Ministry of Supply for permission to publish this work.

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95. *Evidence for the Homolytic Bond Fission of "Positive Halogen" Compounds.*

By ALAN ROBERTSON and WILLIAM A. WATERS.

Catalysis of the autoxidation of tetralin provides evidence for the homolysis of many types of "positive halogen" compounds to free neutral radicals. Halogen compounds, such as *N*-chloroamides, which liberate iodine immediately from hydrogen iodide are immediate catalysts of the autoxidation of tetralin, and consequently are considered to decompose thermally to free halogen atoms and free organic radicals, both of which are active dehydrogenating agents. With many less active compounds the catalysis is more evident

after an induction period, and in this case a second peroxide-catalysed chain reaction is thought to be involved.

The direct action between tetralin and certain of these halogen compounds has been studied, under nitrogen, and the results substantiate the theory of homolysis of the active halide and subsequent dehydrogenation of tetralin by the resulting active radicals.

"Positive halogen" compounds, *e.g.*, types (I)—(V), which are characterised experimentally by liberation of iodine from hydriodic acid (1), are so called because they can be represented as acting by heterolytic bond fission to give halogen cations, rather than halogen anions, as in (2);

Ar·NCl·COR	$CH_2Cl·COR$	$CR_1R_2Cl·NO_2$	Ph·CHBr·CN
(I.)	(II.)	(III.)	(IV.)

$$CH(CO_2Et)_2Br + 2HI \longrightarrow CH_2(CO_2Et)_2 + I_2 + HBr \quad . . . . . (1)$$

$$CH(CO_2Et)_2Br \longrightarrow \bar{C}H(CO_2Et)_2 + Br^+ \quad . . . . . (2)$$
$$Br^+ + 2I^- \longrightarrow Br^- + I_2$$

but whilst it can be shown that the organic radicals which promote reactions of type (1) are invariably groups of strong electron-attracting power, which must markedly diminish the normal tendency for a covalent halogen compound to split, on activation, to yield a stable halogen anion, yet it does not necessarily follow that bond fission of the converse type (*e.g.*, 2) is the only possible alternative. Indeed, theoretical calculations (compare Waters, *J.*, 1933, 1551; 1942, 153) show that in several typical "positive halogen" compounds, the inductive and mesomeric effects of the essential organic substituents do little more than *neutralise* the incipient polarisation of C⁻Halogen, or N⁻Halogen links, and hence a homolytic type of bond

$$CR_1R_2R_3—Hal \longrightarrow ·CR_1R_2R_3 + ·Hal \quad . . . . . (3)$$

fission (3), giving rise to a neutral organic radical and an uncharged halogen atom, may well, in these compounds, require considerably less activation energy than any heterolytic dissociation.

Although the stoicheiometry of reactions involving "positive halogen" compounds does not allow one to discriminate between the heterolytic and the homolytic mechanism of bond fission, certain of their reactions, particularly in solvents of low ionising power, are indicative of the presence of free halogen atoms. Thus (*a*) *N*-chloroamides (I), like diazonium chlorides, readily react with metals such as mercury in several anhydrous solvents (Waters, *J.*, 1937, 2011); (*b*) α-halogenated ketones (II) can, like organic peroxides, catalyse the "abnormal" addition of hydrogen bromide to olefins (Rust and Vaughan, *J. Org. Chem.*, 1942, **7**, 491); and (*c*) *N*-halogeno-amides (I) can substitute olefinic compounds in the α-methylenic position (Ziegler *et al.*, *Annalen*, 1942, **551**, 80) in a manner characteristic of the free neutral radicals or of molecular oxygen (compare Bloomfield, *J.*, 1944, 114: Waters, *Nature*, 1944, **154**, 772).

Though the characteristic reactions of the "positive halogen" compounds can be depicted as processes of homolytic type, it does not necessarily follow from experimental evidence hitherto presented that they all actually do involve the disruption of an organic molecule and the liberation of *free* radicals. Very many organic reactions have proved to be solvolytic processes, or bimolecular reactions, in which bond fission, and any consequent electron transference, occurs without the separation of any "free" radical or ion, and there is no *a priori* method of computation which will decide whether or not a homolytic bond fission requires less activation energy than a bimolecular or multimolecular reaction. Some diagnostic experimental evidence for the occurrence of complete homolytic bond fission with certain "positive halogen" compounds is, however, presented below.

Catalysis of the chain reaction between tetralin and oxygen, which may be summarised by equations (4)—(6), has already been used by us (*Trans. Faraday Soc.*, 1946, **42**, 201; Waters, *ibid.*, p. 184; *J.*, 1946, 1151) as evidence for the production of *free* radicals by dehydrogenation:

$$X· + C_{10}H_{12} \longrightarrow X–H + ·C_{10}H_{11} \quad . . . . . (4)$$

$$·C_{10}H_{11} + O_2 \longrightarrow C_{10}H_{11}–O–O· \quad . . . . . (5)$$

$$C_{10}H_{11}–O–O· + C_{10}H_{12} \longrightarrow C_{10}H_{11}–O–O–H + C_{10}H_{11}· \quad . . . . . (6)$$

and since it has been abundantly shown (compare Waters, "The Chemistry of Free Radicals", Oxford, 1946) that both free halogen atoms and free hydrocarbon radicals are hydrogen abstractors, as depicted by X· of equation (4), it follows that catalysis of the autoxidation of tetralin by positive halogen compounds affords a more conclusive proof of homolytic bond fission of the latter than does the occurrence of reactions of types (*a*) to (*c*) above.

TABLE I.

Catalysis of the autoxidation of tetralin by N-*halogeno-amides and -imides.*

Rate of oxygen uptake (ml. per 15 mins. per 25 ml. of tetralin).

Compound (1 g. added).	Time from start of autoxidation, mins. 0—15.	15—30.	45—60.	105—120.
Tetralin (reference blank)	1	1	1·6	2·0
N : 2 : 4-Trichlorobenzanilide	21	23	23	20
N : 2 : 4 : 6-Tetrachlorobenzanilide	15	19	18	15
N-Bromosuccinimide	11	12	11	6
Bis-*N* : 2 : 4 : 6-tetrachlorocarbanilide	9	11	3	—
N-Bromophthalimide	5	3	1	—
N-Chloroacetanilide	1	2	2	2·5
N : 2 : 4 : 6-Tetrachloroacetanilide	1	2	2	—

TABLE II.

Catalysis of the autoxidation of tetralin by " positive " C-halogen compounds.

Rate of oxygen uptake (as for Table I).

Compound.	Time from start of autoxidation, mins. 0—15.	15—30.	45—60.	105—120.
Ethyl α-bromomalonate	21	19	15	11
Chloropicrin	14	20	19	14
α-Bromobenzyl cyanide	15	14	12	10
p-Phenylphenacyl chloride	9	15	13	—
Bromonitroform	14	13	7	6
Chloroacetone	3	8	14	14
1-Chloro-1-nitropropane	2	4	7	10
ω-Tribromoquinaldine	3	6	10	11
Chlorotrinitromethane	5	5	5	3
α-Bromophenylacetamide	2	5	8	7
ω-Chloro-*p*-nitroacetophenone	2	3	4	5
Phenyl chloromethyl sulphone	2	3	3	—
2-Chloro-2-nitropropane	1·0	1·0	1·0	—
s-Dichloroacetone	1·0	1·0	1·0	—
(Comparison substances.)				
Ethyl malonate	1·0	1·0	1·0	—
Ethyl phenylacetate	1·0	2·0	2·0	—

TABLE III.

Alkyl, acyl, and aryl halides.

Rate of oxygen uptake (as for Table I).

Compound.	Time from start of autoxidation, mins. 0—15.	15—30.	45—60.	105—120.
Benzyl bromide	9	15	17	14
Benzyl chloride	3	6	7	11
Ethyl bromoacetate	11	14	12	11
Ethyl dichloroacetate	1	4	12	14
Triphenylmethyl chloride	2	2	3	—
*cyclo*Hexyl chloride	2	3	3	—
α-Chloronaphthalene	3	3	4	—
Chlorobenzene	2	2	2	—
Benzoyl chloride	1	1	1	—
Ethyl chloroacetate	1	1	1	—
Hexachloroethane	2	3	3	—

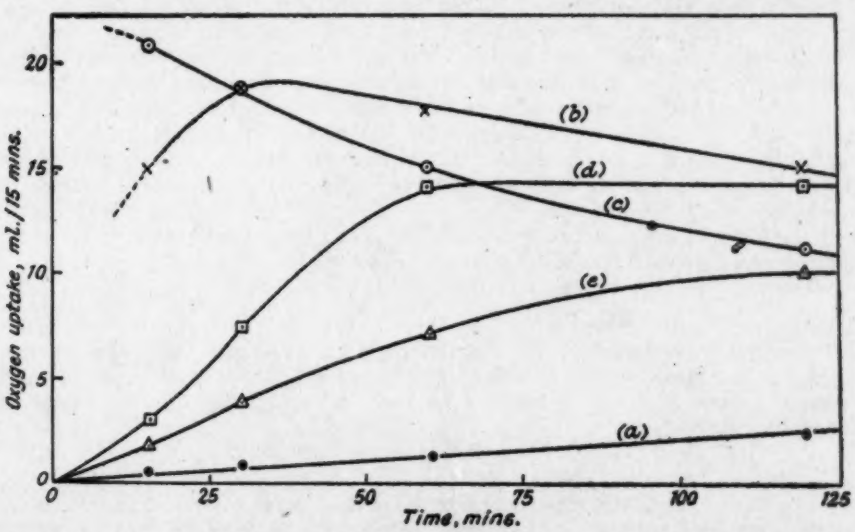
The experimental results (*see* Tables I—III) show that " positive halogen " compounds of the widely varying types (I)—(V) do all act as immediate catalysts for the autoxidation of tetralin at 76°, and resemble therefore substances like dibenzoyl peroxide and benzene diazoacetate. Typical data are more clearly illustrated by the figure, in which, to show the salient features of this catalysis the *rate* of oxygen uptake by tetralin has been plotted against time.

Although freshly distilled tetralin has an exceedingly small initial rate of oxygen uptake, which slowly increases during a prolonged " induction period " (curve *a*) even when no special precautions have been taken to remove traces of adventitious catalysts, yet the addition of 3—4% of an *active* chlorinating agent, such as *N* : 2 : 4 : 6-tetrachlorobenzanilide (type I),

immediately brings about oxygen absorption at a high rate (curve *b*). This high autoxidation rate is maintained for a long period, but eventually declines somewhat, probably because the homolytic dissociation of the *N*-halogen compound (reaction 3) produces progressively fewer and fewer chain-starting active fragments (X· of equation 4) as time goes on, and, in this capacity, is not adequately replaced by tetralin hydroperoxide, which is the main chain-starting agent concerned in the autoxidation of tetralin once the induction period is over (Robertson and Waters, *loc. cit.*).

Substances like ethyl α-bromomalonate (V) (which gave curve *c*), chloropicrin (III; $R_1 = R_2 = Cl$), and α-bromobenzyl cyanide (IV), which react very rapidly with potassium iodide in acetic acid, are also of this type. Corresponding halogen-free compounds, *e.g.*, ethyl malonate, were found to be quite inactive.

In contrast to these highly reactive substances, a number of halogen compounds which react slowly, if at all, with acidified potassium iodide give curves of the general type (*d*), in which the rate of oxygen uptake by tetralin, though always considerably greater than that of the untreated hydrocarbon, at first increases with time. Compounds such as chloroacetone (II; R = Me) (curve *d*), 1-chloro-1-nitropropane (curve *e*), benzyl bromide, and benzyl chloride, are of this type. This action is just that to be expected of a substance which undergoes



homolysis (equation 3) very slowly, for then the enhanced rate of autoxidation could be due to the added effect of the accumulating tetralin hydroperoxide.

It would, however, be an over-simplification to consider only unimolecular dissociations of halogen compounds. Whilst the homolysis of many halides, such as benzyl bromide, may be more facile than their heterolysis in non-ionising solvents of low dielectric constant (compare Waters, *J.*, 1942, 153) such as tetralin, a unimolecular dissociation, *e.g.*, (7), is not the only

$$C_6H_5{\cdot}CH_2{\cdot}Br + \text{Energy} \longrightarrow C_6H_5{\cdot}CH_2{\cdot} + Br{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

process which could decompose them to free radicals. A trace of any other radical-producing catalyst might first abstract a halogen atom (equation 8) whereupon there could be formed an

$$X{\cdot} + C_6H_5{\cdot}CH_2{\cdot}Br \longrightarrow X{\cdot}Br + C_6H_5{\cdot}CH_2{\cdot} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

active *free* hydrocarbon radical, capable of initiating the chain process (9) and (10) in which

$$C_6H_5{\cdot}CH_2{\cdot} + C_{10}H_{12} \longrightarrow C_6H_5{\cdot}CH_2{-}H + {\cdot}C_{10}H_{11} \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$${\cdot}C_{10}H_{11} + C_6H_5{\cdot}CH_2Br \longrightarrow C_{10}H_{11}Br + C_6H_5{\cdot}CH_2{\cdot} \quad . \quad . \quad . \quad . \quad (10)$$

free tetralyl radicals ($C_{10}H_{11}$·) would participate, as well as in the concurrent autoxidation chain (5) and (6) which would thereupon occur. If reaction (8) is faster than (4) then the addition of a halide to tetralin will soon accelerate its autoxidation, although subsequently, if reaction (10) is much slower than (5), most of tetralin may be autoxidised and not brominated, and, on account of the occurrence of two competitive chain reactions, the autoxidation rate may never reach a particularly high value.

It must be noted that reaction (8), though bimolecular, still requires the homolysis of the halogen bond. Peroxide-catalysed addition and substitution reactions involve processes such as (8), and it may be suggested that with several of the less active halogen compounds cited in Tables I—III homolysis occurs, not by unimolecular dissociation (equation 3), but by reaction (8), in which the minute trace of tetralin hydroperoxide present in the tetralin used provides the radicals X· which act as a trigger to all the subsequent chemical changes. Support for this hypothesis is available elsewhere. Kharasch and Mayo (*J. Org. Chem.*, 1937, **2**, 76; *J. Amer. Chem. Soc.*, 1937, **59**, 1655), for instance, have shown that carbon tetraiodide and α-bromoaceto-acetic ester, which are typical compounds of this group, are stable except in the presence of traces of oxygen, or of peroxides, whilst, more recently, Karrer and Schmid (*Helv. Chim. Acta*, 1946, **29**, 525) have shown that substitution in the α-methylenic position by means of *N*-bromosuccinimide is considerably accelerated by adding a little dibenzoyl peroxide to the reaction mixture.

To provide further evidence of the occurrence of reactions (9) and (10), certain of the reactions between tetralin and active halogen compounds have been studied in the absence of air. Tetralin, in carbon tetrachloride solution under a nitrogen atmosphere, reacts easily with *N* : 2 : 4-trichlorobenzanilide. Dichlorobenzanilide is precipitated, and the residual liquid, on careful fractionation, continually evolves hydrogen chloride, leaving 1 : 2-dihydronaphthalene, together with its polymer. When refluxed for some hours with tetralin under the same conditions, ethyl α-bromomalonate reacts slowly with evolution of hydrogen bromide. Ethy malonate could be isolated from the residual liquid, which also gave positive tests for both dihydronaphthalene and ethanetetracarboxylic ester. Reactions of dihydronaphthalene were also exhibited by the dark liquid obtained by prolonged refluxing of tetralin with benzyl bromide under nitrogen. Under these experimental conditions both tetralyl chloride and tetralyl bromide decompose to the corresponding halogen acid and 1 : 2-dihydronaphthalene (compare Bamberger, *Ber.*, 1890, **23**, 197).

Whilst the figures quoted in Tables I—III only give approximate relative values of reaction rates, they show very clearly the effect of structure on the ease of homolysis of both C–Halogen and N–Halogen bonds, and substantiate the form of the equation

$$E_{\text{Homolysis}} = E_{\text{Quantum forces}} + E_{\text{Coulombic forces}}$$

suggested previously (Waters, *loc. cit.*) for the activation energy of the changes involved. It will be seen that homolysis of C–Br is evidently more facile than that of C–Cl, and that substances which readily ionise ($E_{\text{Coulombic forces}}$ high), such as alkyl and acyl chlorides, have but little tendency to react homolytically.

Experimental.

Catalysis of the Autoxidation of Tetralin.—Autoxidation was studied in a 100-ml. "Pyrex" flask, fitted with a small tap-funnel, and a side tube leading, by a flexible joint, to a butyl phthalate manometer and a gas burette. The flask was shaken, at constant rate, in an oil-bath surrounded by a larger vessel of refluxing carbon tetrachloride, which kept the temperature steadily at 76°. For each test there were taken 25 ml. of tetralin which had been purified by fractionation up a column equivalent to 100 theoretical plates, and then had been redistilled at 15—20 mm. in a nitrogen atmosphere soon before use. Air was displaced from the system by evacuating at a water-pump and flushing several times with oxygen, drawn from a cylinder, and the initial rate of autoxidation of each batch of tetralin was first determined (this was always under 1 ml. per 15 min. and corresponded to a very slowly accelerating part of the "induction period", from which peroxide formation was just detectable). 1 G. of a solid halogen compound, or 1 ml. of a liquid, was then added, and after replacing air by oxygen, as before, the new rate of oxygen absorption was followed, at atmospheric pressure, for at least 2 hours. Tables I—III summarise averaged results, and indicate the order of the changes observed. They do not represent absolute measurements of reaction velocity.

Recently purified halogen compounds were used throughout. For instance, in the case of the benzyl chloride, to obviate the possible effect of catalysis due to a trace of benzaldehyde or its peroxide, the material was prepared from aldehyde-free (bisulphite washed) benzyl alcohol by the action of concentrated hydrochloric acid.

Reaction between Tetralin and N : 2 : 4 : 6-*Tetrachlorobenzanilide.*—0·1 Mol. of *N*-chloroamide, 0·5 mol. of tetralin, and 75 ml. of dry carbon tetrachloride were refluxed together for 2 hours under nitrogen. A small amount of hydrogen chloride was evolved. On removal of the carbon tetrachloride under reduced pressure trichlorobenzanilide separated in theoretical yield. The residual liquid was fractionated at 15 mm. pressure, giving fractions (*a*) b. p. 86°, consisting mainly of tetralin, (*b*) b. p. 120°, a liquid, from which however hydrogen chloride was evolved during the distillation, and (*c*) b. p. 220—230°, a viscous oil with a pronounced blue fluorescence in ultra-violet light.

Fraction (*a*), unlike pure tetralin, gave a blue colour on treatment with alcoholic sodium hydroxide, and immediately decolourised bromine in chloroform at 0°. After removal of chloroform from the brominated sample the residue, on storage at — 10°, deposited crystals of 1 : 2-dibromo-1 : 2 : 3 : 4-tetrahydronaphthalene, m. p. 73° after recrystallisation from alcohol (compare Hock and Susemihl, *Ber.*, 1933, **66**, 61).

Fraction (*b*) evolved hydrogen chloride at 190°, and the residue also gave the colour reaction and the bromine addition product characteristic of 1 : 2-dihydronaphthalene. Product (*c*) corresponds with the dimer of dihydronaphthalene described by Bamberger (*loc. cit.*) (Found: C, 91·7; H, 7·5. Calc. for $C_{20}H_{20}$: C, 92·3; H, 7·7%).

Fraction (*b*) presumably contains much 1-chloro-1 : 2 : 3 : 4-tetrahydronaphthalene, but attempts to characterise it more conclusively by hydrolysis to α-tetralol and preparation of its phenylurethane were not successful, since further fission to 1 : 2-dihydronaphthalene occurred on treatment with alkali.

N : 2 : 4-Trichlorobenzanilide reacted with tetralin in a similar manner.

Reaction between Tetralin and Benzyl Bromide.—0·1 Mol. of benzyl bromide, 0·5 mol. of tetralin, and 75 ml. of dry carbon tetrachloride were refluxed under nitrogen for 8 hours. The mixture gradually became yellow, and some hydrogen bromide was evolved (acid vapours; reaction with silver nitrate). On distillation at 15 mm. there were obtained (*a*) at 84—88° a mixture of tetralin and benzyl bromide, which gave positive tests for dihydronaphthalene, (*b*) at 140° a fraction which evolved hydrogen bromide during distillation, and which after further heating at 190° gave strong tests for dihydronaphthalene, and (*c*) a small quantity of the viscous polymer, of b. p. *ca.* 220°.

Reaction between Tetralin and Ethyl α-Bromomalonate.—This was carried out under the same conditions as the previous reaction. Fraction (*a*) gave tests for dihydronaphthalene. It was hydrolysed with hot aqueous alkali, and the aqueous solution thus obtained was concentrated, acidified, and treated with sulphuric acid and ethyl alcohol. About 2 g. of ethyl malonate, b. p. 195—198°, were thus obtained, and further characterised by preparation of crystalline malonamide. Fraction (*b*) again gave reactions of unstable bromotetrahydronaphthalene. The residue (*c*) again gave a water-soluble acid upon hydrolysis with alkali. This on treatment with resorcinol and sulphuric acid gave a fluorescein-like product, typical of succinic acid, and therefore may be considered to contain ethanetetracarboxylic acid. The quantity of acid isolated was, however, too small for effective purification.

A considerable amount of hydrogen bromide was evolved during the reaction between tetralin and the bromo-ester.

The authors thank Mr. A. H. Ford-Moore, Mr. D. Ll. Hammick, and Dr. J. G. Bremner for providing specimens of certain of the "positive halogen" compounds examined. One of them (A. R.) thanks Messrs. Imperial Chemical Industries Ltd. (Billingham Division) for assistance in participating in this work.

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96. *Amidines. Part VI. Preparation of 2-Substituted 4 : 5-Dihydroglyoxalines and Ring Homologues from Cyanides and Alkylenediamines.*

By P. OXLEY and W. F. SHORT.

2-Substituted 4 : 5-dihydroglyoxalines are produced in good yield by heating cyanides with a salt of ethylenediamine. Ring homologues containing 6 and 7 atoms can be prepared similarly, but not those containing 8 and 9 atoms.

DERIVATIVES of 4 : 5-dihydroglyoxaline substituted in position 2 have recently come into prominence owing to their influence on the circulatory system. Thus, 2-benzyldihydroglyoxaline is a powerful vasodilator (Hartmann and Isler, *Arch. exp. Path.*, 1939, **192**, 141) and replacement of the phenyl by a naphthyl radical affords 2-α-naphthylmethyldihydroglyoxaline which is a strong vasoconstrictor (Hartmann and Isler, *loc. cit.*; Hild, *Schweiz. med. Wschr.*, 1941, **71**, 557; Babel, *ibid.*, p. 561). 2-(2′ : 3′ : 4′-Trimethoxybenzyl)dihydroglyoxaline has a pressor action and has been used to combat the fall of blood pressure in spinal anæsthesia and for the treatment of post-operative shock (Jones and Wilson, *Lancet*, 1938, **234**, 195; Hartmann and Isler, *loc. cit.*; Elmes and Jefferson, *Brit. Med. J.*, 1942, ii, 65; Burn, *Brit. Med. Bull.*, 1946, **4**, 95). Since relatively few methods are available for the preparation of dihydroglyoxalines (see Chitwood and Reid, *J. Amer. Chem. Soc.*, 1935, **57**, 2424; Scholtz, *Ind. Eng. Chem.*, 1945, **37**, 120) we were led to inquire whether these compounds could be obtained by adapting and extending the methods for the preparation of amidines described in previous parts of this series.

It was shown in Part I (Oxley and Short, *J.*, 1946, 147) that amidines can be prepared by heating a cyanide with an ammonium sulphonate, and we now find that 2-substituted dihydroglyoxalines are obtained from a cyanide and a neutral sulphonate of ethylenediamine at 220—250° :

$$\overset{\oplus}{N}H_3\cdot CH_2\cdot CH_2\cdot \overset{\oplus}{N}H_3 + R\cdot CN \longrightarrow \left.\begin{matrix} CH_2{-}NH \\ | \\ CH_2{-}NH \end{matrix}\right\rangle CR \Big\}^{\oplus} + \overset{\oplus}{N}H_4$$

When two molecular proportions of the cyanide are used, a considerable quantity of an amidinium

salt $R{\cdot}C(:NH){\cdot}NH_2\}^{\oplus}\ R'{\cdot}\overset{\ominus}{SO_3}$ is simultaneously produced by the reaction between the cyanide and the ammonium salt formed in the ring closure. The heterocyclic nucleus is formed so readily that attempts to isolate the intermediate amidinium salt,

$$R{\cdot}C(:NH){\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2\}^{\oplus}\ R'{\cdot}\overset{\ominus}{SO_3},$$

were unsuccessful. Ring formation is prevented by the introduction of alkyl groups, and Mr. J. Miller obtained the *toluene*-p-*sulphonates* of *N*-β-diethylaminoethylbenzamidine and *N*-β-diethylaminoethyl-*p*-amidinophenyl methyl sulphone by heating β-diethylaminoethylammonium toluene-*p*-sulphonate with phenyl cyanide and *p*-cyanophenyl methyl sulphone respectively.

In a subsequent communication it will be shown that the production of amidines by the addition of ammonia or an amine to a cyanide is facilitated by (*a*) structural influences which enhance the kationoid properties of the carbon atom of the cyano-group, and (*b*) increase in the strength of the basic addendum. Owing to the instability of unsubstituted amidines, only exceptional cyanides yield amidines by combination with ammonia in absence of a stabilising agent (cf. Part I, *loc. cit.*). However, *N*-alkylamidines are known to be less readily decomposed to cyanides than the corresponding unsubstituted amidines (cf. Part III, this vol., p. 382) and it is clear that combination of a cyanide with ethylenediamine to give an amidine, $NH{:}CR{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$, would be favoured by the strongly basic character of the diamine and by the presence of the methylene chain. Since ring closure by loss of the elements of ammonia would almost certainly be irreversible it seemed probable that dihydroglyoxalines would be formed by boiling cyanides with ethylenediamine. It is now found that reactive cyanides, such as *p*-cyanophenyl methyl sulphone, rapidly yield dihydroglyoxalines with boiling ethylenediamine but the slow reaction which occurs with less active cyanides cannot conveniently be accelerated by raising the temperature owing to the low boiling point of the diamine (117°) and the evolution of ammonia. In such cases it is advantageous to use the mono-acid salt of the diamine which reacts rapidly with cyanides at 100—200° to give dihydroglyoxalinium salts and ammonia:

$$\overset{\oplus}{N}H_3{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2 + R{\cdot}CN \longrightarrow \left.\begin{matrix} CH_2{-}NH \\ | \\ CH_2{-}NH \end{matrix}\!\!>\!CR\right\}^{\oplus} + NH_3$$

The use of sulphonic acid salts facilitates reaction with the cyanides since a homogeneous melt is formed, and, although the corresponding chlorides ultimately afford good yields of dihydroglyoxalines, the initial reaction mixture is usually heterogeneous, the reaction is slower, and the resulting hydrochlorides are not so tractable as the sulphonates. The scope of the method is illustrated by the examples collected in the Table (Nos. 1—25) and it will be observed that bases containing two dihydroglyoxaline nuclei are readily prepared from dicyanides (Nos. 18—25). The yields are so good that the method could be used for the identification of cyanides.

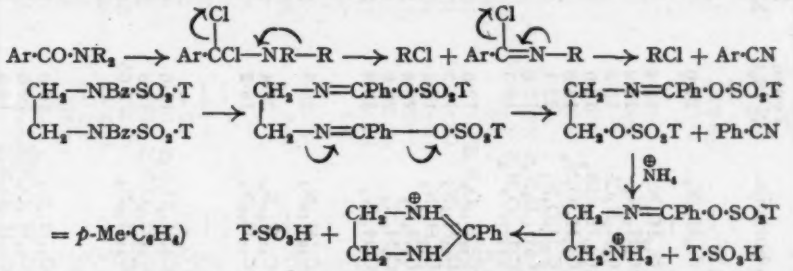
Mixed imides, $Ar{\cdot}SO_2{\cdot}NX{\cdot}CO{\cdot}R$, and ammonium salts, $YZ\overset{\oplus}{N}H_2\}\overset{\ominus}{A}$, afford salts of amidines, $R{\cdot}C(:NX){\cdot}NYZ$ (Part III, *loc. cit.*), and we now find that *N*-benzoylbenzenesulphonmethylamide and ethylenediammonium dichloride yield 2-phenyldihydroglyoxaline and *NN'*-dimethylbenzamidine:

$$Ph{\cdot}SO_2{\cdot}NMe{\cdot}CO{\cdot}Ph \longrightarrow Ph{\cdot}SO_2{\cdot}O{\cdot}CPh{:}NMe \xrightarrow{(CH_2\overset{\oplus}{N}H_2)_2} Ph{\cdot}SO_2H + \overset{\oplus}{N}H_2{-}CH_2{-}CH_2{-}NH{\cdot}CPh{:}\overset{\oplus}{N}HMe \longrightarrow PhC(:\overset{\oplus}{N}HMe){\cdot}NHMe + Ph{\cdot}SO_2H$$

$$\overset{\oplus}{N}H_2{-}CH_2{-}CH_2{-}NH{\cdot}CPh{:}\overset{\oplus}{N}HMe \longrightarrow \left.\begin{matrix} CH_2{-}NH \\ | \\ CH_2{-}NH \end{matrix}\!\!>\!CPh\right\}^{\oplus} + Me{\cdot}\overset{\oplus}{N}H_2$$

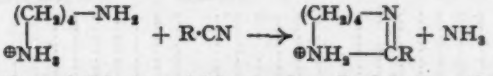
The potassium salt of αβ-bistoluene-*p*-sulphonamidoethane (Howard and Marckwald, *Ber.*, 1899, **32**, 2041) and benzoyl chloride afford NN'-*dibenzoyl*-αβ-*bistoluene*-p-*sulphonamidoethane*, and 2-phenyldihydroglyoxaline (93%) and phenyl cyanide are obtained when this mixed imide is heated with ammonium toluene-*p*-sulphonate. We suggest that in this reaction the toluene-*p*-sulphonyloxy-radical simulates the behaviour of the chlorine atom in v. Braun's method for

the preparation of aryl cyanides and chloroparaffins (or αω-dichloroparaffins) from the *N*-disubstituted amido-chlorides of aromatic acids (*Ber.*, 1904, **37**, 2812, 2915, 3210).



So little is known of the ring homologues of dihydroglyoxaline that it seemed desirable to ascertain whether they could be prepared from cyanides and salts of aliphatic diamines. Derivatives of 3 : 4 : 5 : 6-tetrahydropyrimidine substituted in position 2 have been prepared (*a*) from trimethylene dibromide and amidines (Pinner, *Ber.*, 1893, **26**, 2122; Branch and Titherley, *J.*, 1912, **101**, 2342), (*b*) by heating diacyltrimethylenediamides in a stream of hydrogen chloride (Hofmann, *Ber.*, 1888, **21**, 2336), (*c*) by fusing trimethylenediammonium dichloride with sodium acetate (Harries and Haga, *Ber.*, 1899, **32**, 1191; Haga and Majima, *Ber.*, 1903, **36**, 333), and (*d*) by heating a mixture of monoacyltrimethylenediamines and calcium oxide under pressure at 250° (Aspinall, *J. Amer. Chem. Soc.*, 1940, **62**, 2160). Methods (*a*)—(*c*) afford low yields (usually a few per cent.) and, although much better yields are obtained by method (*d*), it is somewhat laborious, and only three members of the group have been prepared. Tetrahydropyrimidines can be conveniently prepared from cyanides and trimethylenediamine or its salts and a number of examples are collected in the Table (Nos. 26—31). It will be noted that the method gives compounds containing two tetrahydropyrimidine nuclei when applied to dicyanides.

1-*Phenyl*-2 : 7-*diaza*cyclo*heptene* is obtained in 88% yield from an equimolecular mixture of phenyl cyanide, tetramethylenediamine, and *tetramethylenediammonium bistoluene*-*p*-*sulphonate* at 200°; a number of other members of this group have been prepared, including a compound (No. 36) containing two diaza*cyclo*heptene nuclei (see Table Nos. 32—36).



The only representative of this type hitherto described is 1-methyl-2 : 7-diaza*cyclo*heptene which was obtained in very low yield from tetramethylenediammonium dichloride and sodium acetate at 250° (Haga and Majima, *Ber.*, 1903, **36**, 337).

The practical limit of the method appears to be reached with the formation of diaza*cyclo*heptenes, since attempts to produce 8- and 9-membered ring compounds by condensing penta- and hexa-methylenediamines or their salts with cyanides result in the production of mixtures from which no homogeneous solid derivatives can be isolated. The results do not preclude the possibility that in each case 8- and 9-membered ring compounds are formed, but indicate simultaneous formation of condensation products of higher molecular weight, including, for example, substances of the type $NH{:}CR{\cdot}NH{\cdot}[CH_2]_n{\cdot}\{N{:}CR{\cdot}NH{\cdot}[CH_2]_n\}_x{\cdot}N{:}CR{\cdot}NH_2$.

Notes to Table.—Except where otherwise indicated, the experiments were conducted with 0·02—0·1 g.-mol. of cyanide, using one mol. of the monotoluene-*p*-sulphonate of the alkylenediamine (or 0·5 mol. of the base and 0·5 mol. of the bistoluene-*p*-sulphonate) per mol. of cyanide or per 0·5 mol. of dicyanide. Yields are expressed in terms of the cyanide employed. Some of the dihydroglyoxalines described in the patent literature have not been indexed in abstract journals since no analyses were recorded in the patents cited below. Methods for isolating the products are illustrated by typical examples in the experimental section.

(1) Chitwood and Reid (*loc. cit.*) state that the base and its picrate have m. p. 41° and 125·8° respectively.

(2) Other methods of preparation are recorded in the experimental section. The hydrochloride had m. p. 175° (Found: C, 61·3; H, 6·8; N, 14·3. Calc. for $C_{10}H_{13}N_2Cl$: C, 61·1; H, 6·7; N, 14·3%). Ciba (B.P.P., 460,528; 514,411) state that the base and the hydrochloride have m. p. 61—62° and 168—170° respectively. Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 3195) records m. p. 68°, 174°, and 149° for the base, the hydrochloride, and the picrate respectively.

(3) A *dipicrate*, m. p. 195° (decomp.), was also prepared (Found: N, 19·8. $C_{22}H_{19}O_{14}N_8$ requires N, 19·9%). The bistoluene-*p*-sulphonate was a yellow gum considerably more soluble than the mono-acid salt. Sonn and Ciba (B.P. 460,528) state that the dihydrochloride has m. p. 280—285°.

Compound.	Reaction. Temp.	Time (hrs.).	Yield (%).	Base. M. p.	Formula.	Found, N (%).	Req., N (%).
(1) 2-*n*-Butyldihydroglyoxaline	160°	5	96	41·4°	—	—	—
(2) 2-Benzyldihydroglyoxaline	200	1	91	66—68	—	—	—
(3) 2-(4′-*Aminobenzyl*)*dihydroglyoxaline*	140	6	74	124	$C_{10}H_{13}N_3$	24·0	24·0
(4) 2-(4′-Sulphamidobenzyl)dihydroglyoxaline	180	2¼	100	—	—	—	—
(5) 2-(1′-*Naphthylmethyl*)*dihydroglyoxaline*	175—200	1	99	119·5	$C_{14}H_{14}N_2$	13·4	13·3
(6) 2-Phenyldihydroglyoxaline	100	112	44	101	$C_9H_{10}N_2$	18·9	19·2
(7) 2-(4′-*Chlorophenyl*)*dihydroglyoxaline*	160	1	90	187	$C_9H_9N_2Cl$	15·5	15·5
(8) 2-p-*Anisyldihydroglyoxaline*	200	1½	72	140	$C_{10}H_{12}ON_2$	16·0	15·9
(9) 2-(3′ : 4′-*Dimethoxyphenyl*)*dihydroglyoxaline*	200	1	34	158·5	$C_{11}H_{14}O_2N_2$	13·6	13·6
(10) 2-(2′-*Nitrophenyl*)*dihydroglyoxaline*	160	1	74	98	$C_9H_9O_2N_3$	22·1	22·0
(11) 2-(4′-*Sulphophenyl*)*dihydroglyoxaline*	160	¼	97	>360	$C_9H_{10}O_5N_2S$	12·0	12·4
(12) 2-(4′-*Sulphonamidophenyl*)*dihydroglyoxaline*	160—225	½	81	245 (decomp.)	$C_9H_{11}O_4N_3S$	18·5	18·6
(13) 2-(4′-*Methylsulphonylphenyl*)*dihydroglyoxaline*	200	½	89	213·5	$C_{10}H_{12}O_3N_2S$	12·5	12·5
(14) 2-α-*Naphthyldihydroglyoxaline*	200	3	66	133·5—134	$C_{13}H_{12}N_2$	14·3	14·3
(15) 2-β-*Naphthyldihydroglyoxaline*	160	2	75·5	118	$C_{13}H_{12}N_2$	14·4	14·3
(16) 2-α-*Pyridyldihydroglyoxaline*	200	¼	95	98·5—99	$C_8H_9N_3$	28·8	28·6
(17) 2-β-*Pyridyldihydroglyoxaline*	200	¼	96	111—111·5	$C_8H_9N_3$	28·6	28·6
(18) 1 : 2-*Bis*-(2′-*dihydroglyoxalinyl*)*ethane*	150—200	½	99	235 (decomp.)	$C_8H_{14}N_4$	33·6	33·7
(19) 1 : 3-Bis-(2′-dihydroglyoxalinyl)propane	170—200	1	84	—	—	—	—
(20) 1 : 4-Bis-(2′-dihydroglyoxalinyl)butane	170—200	1	93	218·5—219	$C_{10}H_{16}N_4$	28·6	28·9
(21) 1 : 5-Bis-(2′-dihydroglyoxalinyl)pentane	170—200	1	96	—	—	—	—
(22) 1 : 8-Bis-(2′-dihydroglyoxalinyl)octane	175—225	1½	93	187·5	$C_{14}H_{26}N_4$	22·4	22·4
(23) 1 : 11-*Bis*-(2′-*dihydroglyoxalinyl*)*undecane*	175—225	1½	91	162·5	$C_{17}H_{32}N_4$	19·2	19·2
(24) 4 : 4′-Bis-(2-dihydroglyoxalinyl)diphenyl	225	½	100	—	—	—	—
(25) 4 : 4′-Bis-(2-dihydroglyoxalinyl)stilbene	200—245	½	65	—	—	—	—
(26) 2-Phenyl-3 : 4 : 5 : 6-tetrahydropyrimidine	140	½	94·5	86—87	—	—	—
(27) 2-(4′-*Sulphophenyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	160	½	98	>360	$C_{10}H_{12}O_3N_2S$	11·6	11·7
(28) 2-(4′-*Methylsulphonylphenyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	255	1½	71	173·5	$C_{11}H_{14}O_2N_2S$	11·8	11·8
(29) 2-(1′-*Naphthylmethyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidine*	165—225	2	95	124	$C_{15}H_{16}N_2$	12·65	12·5
(30) 2-α-Pyridyl-3 : 4 : 5 : 6-tetrahydropyrimidine	200	1½	96	*ca.* 15	—	—	—
(31) 1 : 2-Bis-(2′-tetrahydropyrimidyl)ethane	140	½	94·5	—	—	—	—
(32) 1-Benzyl-2 : 7-diaza*cyclo*heptene	200	2	99	—	—	—	—
(33) 1-*Phenyl*-2 : 7-*diaza*cyclo*heptene*	200	1	88	105	$C_{11}H_{14}N_2$	16·0	16·1
(34) 1-(4′-*Sulphophenyl*)-2 : 7-*diaza*cyclo*heptene*	160	¼	83	>360	$C_{11}H_{14}O_3N_2S$	10·6	11·0
(35) 1-(4′-*Methylsulphonylphenyl*)-2 : 7-*diaza*cyclo*heptene*	200	1	83	175	$C_{12}H_{16}O_2N_2S$	10·9	11·1
(36) 1 : 4-Bis-(2′ : 7′-diaza*cyclo*heptenyl)butane	200	1	30	—	—	—	—

	Picrate.				Toluene-*p*-sulphonate.			
	M. p.	Formula.	Found, N (%).	Req., N (%).	M. p.	Formula.	Found, N (%).	Req., N (%).
(1)	126°	$C_{13}H_{17}O_7N_5$	19·75	19·7	98°	$C_{14}H_{22}O_3N_2S$	9·45	9·4
(2)	148·5	$C_{16}H_{15}O_7N_5$	17·8	17·9	91	$C_{17}H_{20}O_3N_2S$	8·3	8·4
(3)	138·5	$C_{16}H_{16}O_7N_6$	21·0	20·8	190	$C_{17}H_{21}O_3N_3S$	12·3	12·1
(4)	168·5	$C_{16}H_{16}O_9N_6S$	18·1	17·95	213—213·5	$C_{17}H_{21}O_5N_3S_2$	10·2	10·2
(5)	197	$C_{20}H_{17}O_7N_5$	16·2	15·9	143·5	$C_{21}H_{22}O_3N_2S$	7·5	7·3
(6)	242	$C_{15}H_{13}O_7N_5$	18·8	18·7	165	$C_{16}H_{18}O_3N_2S$	9·0	8·8
(7)	206—206·5	$C_{15}H_{12}O_7N_5Cl$	17·0	17·1	218	$C_{16}H_{17}O_3N_2ClS$	7·9	7·95
(8)	209	$C_{16}H_{15}O_9N_5$	17·3	17·3	201	$C_{17}H_{20}O_4N_2S$	8·15	8·05
(9)	206	$C_{17}H_{17}O_9N_5$	16·2	16·1	—	—	—	—
(10)	185	$C_{18}H_{12}O_9N_6$	20·1	20·0	—	—	—	—
(11)	—	—	—	—	—	—	—	—
(12)	—	—	—	—	253·5	$C_{16}H_{19}O_5N_3S_2$	10·4	10·6
(13)	—	—	—	—	265	$C_{17}H_{20}O_5N_3S_2$	7·1	7·1
(14)	246	$C_{19}H_{15}O_7N_5$	16·5	16·5	—	—	—	—
(15)	205	$C_{19}H_{15}O_7N_5$	16·3	16·5	190	$C_{20}H_{20}O_3N_2S$	7·5	7·6
(16)	235	$C_{14}H_{12}O_7N_6$	22·3	22·3	145—146	$C_{15}H_{17}O_3N_2S$	12·7	13·2
(17)	216·5	$C_{20}H_{15}O_{14}N_9$	20·8	20·8	172	$C_{15}H_{17}O_3N_2S$	12·9	13·2
(18)	—	—	—	—	245	$C_{22}H_{20}O_6N_4S_2$	11·1	11·0
(19)	—	—	—	—	148	$C_{23}H_{22}O_6N_4S_2$	10·8	10·7
(20)	—	—	—	—	176	$C_{24}H_{24}O_6N_4S_2$	10·4	10·4
(21)	—	—	—	—	157	$C_{25}H_{26}O_6N_4S_2$	10·1	10·15
(22)	—	—	—	—	161—161·5	$C_{26}H_{42}O_6N_4S_2$	9·4	9·4
(23)	—	—	—	—	161·5—162	$C_{31}H_{44}O_6N_4S_2$	8·7	8·8
(24)	—	—	—	—	*ca.* 375 (decomp.)	$C_{22}H_{24}O_6N_4S_2$	8·9	8·8
(25)	—	—	—	—	347	$C_{24}H_{26}O_6N_4S_2$	8·5	8·5
(26)	180·5	$C_{16}H_{13}O_7N_5$	18·2	18·0	122·5	$C_{17}H_{20}O_3N_2S$	8·5	8·4
(27)	—	—	—	—	—	—	—	—
(28)	—	—	—	—	187	$C_{16}H_{22}O_5N_2S_2$	6·8	6·8
(29)	258 (decomp.)	$C_{21}H_{19}O_7N_5$	15·5	15·45	183·5	$C_{22}H_{24}O_3N_2S$	7·1	7·1
(30)	186·5	$C_{15}H_{14}O_7N_6$	21·6	21·5	—	—	—	—
(31)	—	—	—	—	285	$C_{24}H_{24}O_6N_4S_2$	10·5	10·45
(32)	131	$C_{18}H_{19}O_7N_5$	16·8	16·8	—	—	—	—
(33)	184	$C_{17}H_{17}O_7N_5$	17·2	17·4	153—153·5	$C_{18}H_{22}O_3N_2S$	8·2	8·1
(34)	—	—	—	—	—	—	—	—
(35)	186	$C_{18}H_{19}O_9N_5S$	14·65	14·55	184	$C_{19}H_{24}O_5N_2S$	6·8	6·6
(36)	—	—	—	—	85	$C_{23}H_{42}O_6N_4S_2$	9·0	9·2

(4) The toluene-*p*-sulphonate crystallised unchanged from 2N-sodium carbonate, and the dihydroglyoxaline was not extracted by chloroform from a solution of the salt in one equivalent of N-sodium hydroxide.

(5) The temperature was 175—180° during the first ½ hour and 200° during the second ½ hour. 1-Naphthylmethyl cyanide and the monohydrochloride of ethylenediamine (1 mol.) afforded a 71% yield of the dihydroglyoxaline after 1½ hours at 180—185°, and unchanged cyanide (24%) was recovered. 2-(1′-*Naphthylmethyl*)*dihydroglyoxalinium chloride* had m. p. 258—259° (Found: N, 11·3; Cl, 14·3. $C_{14}H_{15}N_2Cl$ requires N, 11·4; Cl, 14·4%). Ciba (B.PP. 460,528; 514,411) record 119—120° and 252—253° as the m. p. of the base and the hydrochloride respectively.

(6) The low temperature was employed in an unsuccessful attempt to isolate the intermediate amidine. This dihydroglyoxaline was also prepared from ethylenediammonium dichloride and the bistoluene-*p*-sulphonate (see Experimental section). 2-*Phenyldihydroglyoxalinium benzenesulphonate* had m. p. 141° (Found: N, 9·3. $C_{15}H_{16}O_3N_2S$ requires N, 9·2%). The m. p. of the base is given as 101° by Hofmann (*loc. cit.*), Forssel (*Ber.*, 1892, **25**, 2135), and Hill and Aspinall (*J. Amer. Chem. Soc.*, 1939, **61**, 822), and as 100—102° by the I.G. (B.P. 492,812). Hill and Aspinall (*loc. cit.*) state that the picrate has m. p. 244°.

(11) This compound was soluble in aqueous sodium hydroxide and formed no salts with acids.

(12) This compound was soluble in aqueous sodium hydroxide.

(13) Other methods of preparation are described in the Experimental section. 2-(4′-*Methylsulphonylphenyl*)*dihydroglyoxalinium chloride* had m. p. 337° (decomp.) (Found: N, 10·8. $C_{10}H_{13}O_2N_2ClS$ requires N, 10·75%).

(14) 2-α-*Naphthyldihydroglyoxalinium chloride* had m. p. 305—306° (Found: N, 12·1. $C_{13}H_{13}N_2Cl$ requires N, 12·05%). The I.G. (B.P. 492,812) give the m. p. of the base as 136°.

(15) The base is stated to have m. p. 124° by the I.G. (*loc. cit.*). 2-β-*Naphthyldihydroglyoxalinium benzenesulphonate* had m. p. 188·5° (Found: N, 7·9. $C_{19}H_{18}O_2N_2S$ requires N, 7·9%).

(17) The dipicrate separated from a solution containing equimolecular proportions of the base and picric acid. Ciba (B.PP., 460,528; 514,411) state that the base has m. p. 104—105°.

(18) The temperature was 150° for the first 10 minutes and 200° during the final 10 minutes. There is a marked alternation in the m. ps. of the toluene-*p*-sulphonates of the αω-bis(dihydroglyoxalinyl)-alkanes, the odd members having lower m. ps. and much higher solubility in water.

(19) The temperature was kept at 170° for ½ hour and then at 200° for ½ hour. The base was readily soluble in water.

(20) The temperature was kept at 170° for ½ hour and then at 200° for ½ hour. Lehr and Erlenmeyer (*Helv. Chim. Acta*, 1944, **27**, 491) record m. p. 209—210° and 207° for the base and the dipicrate respectively.

(21) After ½ hour at 170°, the temperature was kept at 200° for ½ hour. The base was readily soluble in water.

(22) The temperature was kept at 175° for ½ hour and then at 225° for 1 hour. According to B.P. 501,522 the base has m. p. 185—187°.

(25) The temperature was 200° during the first ½ hour and 245° during the final ½ hour. There was no unchanged cyanide and the crude yield was *ca.* 100%.

(26) Aspinall (*J. Amer. Chem. Soc.*, 1940, **62**, 2160) records m. p. 87° for the base and 181° for the picrate.

(28) Trimethylenediammonium bistoluene-*p*-sulphonate (1 mol.) was used. There was no reaction after an hour at 205°.

(29) The temperature was 165° during 1 hour and 225° during the remaining hour. 2-(1′-*Naphthylmethyl*)-3 : 4 : 5 : 6-*tetrahydropyrimidinium chloride* had m. p. 214° and was dried at 100° before analysis (Found: N, 10·8. $C_{15}H_{17}N_2Cl$ requires N, 10·75%).

(30) Trimethylenediamine was used in this experiment. The free base gave unsatisfactory results on analysis by the Dumas method. The *bistoluene*-p-*sulphonate*, m. p. 65°, afforded a strongly acid solution and was very deliquescent (Found: N, 8·85. $C_{22}H_{27}O_6N_2S_2$ requires N, 8·3%).

(31) The free *base*, obtained from the bistoluene-*p*-sulphonate and sodium hydroxide at 0° and recrystallised from benzene, had m. p. *ca.* 200° (decomp.) (Found: N, 27·9, 28·0. $C_{10}H_{18}N_4$ requires N, 28·9%). This compound was rapidly hydrolysed by cold water or by cold aqueous alkali.

(32) A 16% yield of this compound, b. p. 125—130°/0·7 mm., was obtained by heating the cyanide and tetramethylenediamine (1 mol.) under reflux for 6 hours (bath at 200°) but there was considerable decomposition during distillation.

(35) The picrate first separated from methanol in orange prisms m. p. 155° but changed to yellow needles, m. p. 186°, on crystallisation from ethanol and the low-melting form could not be obtained subsequently.

(36) The bistoluene-*p*-sulphonate crystallised very slowly, the yield quoted being obtained after keeping for a week.

Experimental.*

Preparation of Alkylenediamine Salts.

2-*Aminoethylammonium Toluene*-p-*sulphonate*.—Toluene-*p*-sulphonic acid monohydrate (190 g.) in water (100 c.c.) was neutralised to Congo-red with hydrated ethylenediamine (40 c.c.); more diamine (40 c.c.) was then added and the solution evaporated to dryness on the steam-bath at 5 mm. The residue, recrystallised from *iso*propanol (250 c.c.), afforded 206—218 g. (89—94%) of 2-*aminoethylammonium toluene*-p-*sulphonate*, m. p. 123° (Found: N, 11·8. $C_9H_{16}O_3N_2S$ requires N, 12·1%). This salt is not deliquescent and did not lose an appreciable amount of diamine when heated at 200° in an open vessel. An attempt to prepare the monobenzenesulphonate in the same way resulted in the separation of the neutral salt.

* See also B.P. Applns. 11,156/2·5·1945 and 34,294/18·12·1945.

Ethylenediammonium Bistoluene-p-*sulphonate.*—Neutralisation of toluene-*p*-sulphonic acid to Congo-red with ethylenediamine and crystallisation from 50% aqueous alcohol gave the *diammonium bistoluene*-p-*sulphonate*, m. p. 360° (decomp.) (Found: N, 6·9. $C_{16}H_{24}O_6N_2S_2$ requires N, 6·9%).

Trimethylenediammonium bistoluene-p-*sulphonate* was prepared in the same way as the lower homologue; it crystallised from *iso*propanol in colourless plates, m. p. 251° (Found: N, 6·9. $C_{17}H_{26}O_6N_2S_2$ requires N, 6·7%). Heat was evolved when this salt was added to an equivalent of the diamine, but attempts to crystallise the product from *iso*propanol and other solvents resulted in the isolation of the crystalline bis-sulphonate only.

Tetramethylenediamine and Tetramethylenediammonium Bistoluene-p-*sulphonate.*—The diamine was prepared by the application of the Hofmann reaction to adipodiamide (v. Braun and Lemke, *Ber.*, 1922, **55**, 3529), using a method similar to that employed by Aspinall (*J. Amer. Chem. Soc.*, 1941, **63**, 2843) for the preparation of trimethylenediamine. Adipodiamide (72 g.) was added at 10° to a stirred solution of potassium hypobromite, prepared from bromine (160 g.; 2 mols.), potassium hydroxide (330 g.; 10 mols.), and water (1·5 l.). The temperature rose rapidly to 15° and then to 20° during the next 20 minutes. The clear solution was heated on the steam-bath for 2 hours, then neutralised with concentrated hydrochloric acid (250 c.c.) and evaporated to a small volume. The solution was cooled and filtered, and the salts were washed with 80% aqueous acetone. The filtrate and washings were evaporated almost to dryness, potassium hydroxide (100 g.) and water (25 c.c.) were added, and the mixture was distilled to dryness at 20 mm. The distillate was saturated with potassium hydroxide (60 g.), the layer of oil was separated and diluted with benzene (50 c.c.), and the solution was dried (KOH; 10 g.). The liquid was decanted and distilled from sodium (1 g.), using a short column. A forerunning, b. p. 77—78°, was collected, and tetramethylenediamine then distilled at 158—159° and solidified on cooling to plates, m. p. 27—27·2° (29·8 g.; 67·7%). The forerunning and distillation residue were neutralised to Congo-red with aqueous toluene-*p*-sulphonic acid, the solution was evaporated to dryness, and the residue, crystallised from methanol, gave colourless prisms of *tetramethylenediammonium bistoluene*-p-*sulphonate*, m. p. 224° (Found: N, 6·6. $C_{18}H_{28}O_6N_2S_2$ requires N, 6·5%). The yield was 17·4 g., so that the total yield was equivalent to 75·8% of diamine.

Hexamethylenediammonium bistoluene-p-*sulphonate* crystallised from alcohol in slender needles, m. p. 183° (Found: N, 6·2. $C_{20}H_{32}O_6N_2S_2$ requires N, 6·1%). The heat evolution on mixing this salt with the base indicated the production of a mono-acid salt but this could not be isolated.

Dihydroglyoxalines and Ring Homologues from Cyanides.

The cyanide and alkylenediamine or alkylenediamine salt were heated under reflux until ammonia was no longer evolved, the temperature being regulated so that a steady evolution of gas was maintained. Ammonia was often not evolved until the mixture had been maintained at the reaction temperature for a few minutes. Free diamines and their monotoluene-*p*-sulphonates afforded homogeneous mixtures with cyanides but other salts sometimes afforded heterogeneous mixtures and stirring was necessary to promote rapid reaction. Ethylenediamine gave a monotoluene-*p*-sulphonate which could be isolated, but other mono-salts were not obtained crystalline. When mono-salts could not be isolated, the cyanide was heated with an equivalent mixture of the diamine with either the neutral salt of the diamine or an ammonium salt. When an ammonium salt was employed, the cyanide was usually added after heating the mixture until ammonia was no longer evolved; a slight excess of diamine reduced frothing. When a sulphonate was employed, the corresponding salt of the heterocyclic base was usually isolated from the reaction product by crystallisation from water, or, if too soluble, from ethanol or *iso*propanol. Acetic acid was a suitable solvent in cases (*e.g.*, No. 25) where the sulphonate was too sparingly soluble in water. The hydrochlorides of the heterocyclic bases were usually less tractable than the sulphonates, many being deliquescent, and, when the hydrochloride of a diamine was employed, it was usually preferable to liberate the base from the reaction product by means of 2—3N-sodium hydroxide, collect it in chloroform or benzene, and purify it by distillation, sublimation, or crystallisation. The hydrochloride can then be prepared from the purified base and ethanolic hydrogen chloride.

2-*Benzyldihydroglyoxaline.*—(1) A mixture of benzyl cyanide (5·85 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.; 1 mol.) was maintained at 200° for 1 hour, during which ammonia was evolved. The product was dissolved in water (20 c.c.), made alkaline with 5N-sodium hydroxide, and extracted with chloroform. The residue obtained by evaporating the dried chloroform solution was distilled; the fraction, b. p. 125°/2 mm., afforded 2-benzyldihydroglyoxaline, m. p. 66—68° after recrystallisation from light petroleum (7·3 g.; 91%). The product was characterised by preparing the derivatives recorded in the Table (No. 2). (2) Benzyl cyanide (58·5 g.), ethylenediammonium dichloride (33·25 g.; 0·5 mol.), and ethylenediamine (15 g.; 0·5 mol.) were heated at 200° for 1 hour and then treated as described in (1). The crude base (yield 80%) was distilled and converted into the hydrochloride, m. p. 175°, by means of hydrogen chloride in *iso*propanol. Yield, 66%. (3) A mixture of benzyl cyanide (5·85 g.) and ethylenediamine (3·0 g.; 1·0 mol.) was heated under reflux for 36 hours in a bath at 200° and then distilled under diminished pressure. The first fraction (2 g.), b. p. 79—81°/2 mm., consisted of crude benzyl cyanide; 2-benzyldihydroglyoxaline distilled at 125°/2 mm. and solidified to crystals, m. p. 64—66° (4 g.; 50%). The distillation residue was crystallised from acetic acid and afforded s-*bisphenylacetoethylenediamide* (15%), m. p. 204° (Found: C, 72·8; H, 6·7; N, 9·6. $C_{18}H_{20}O_2N_2$ requires C, 72·9; H, 6·8; N, 9·5%). The production of this amide was probably due to the presence of water in the ethylenediamine.

2-*Phenyldihydroglyoxaline.*—(1) A mixture of phenyl cyanide (10·3 g.) and ethylenediammonium bistoluene-*p*-sulphonate (20·2 g.; 0·5 mol.) was heated in a sealed tube for 60 hours at 270°. The product was dissolved in hot water and the crystals (6·0 g.; 20%) which separated on cooling were identified as benzamidinium toluene-*p*-sulphonate, m. p. and mixed m. p. 195° (Found: N, 9·8. Calc. for $C_{14}H_{16}O_3N_2S$: N, 9·6%). The filtrate was extracted with benzene to remove a little phenyl cyanide, and the aqueous solution was then made alkaline with sodium hydroxide. The oil which separated was collected in chloroform and afforded on distillation a fraction, b. p. 162°/5 mm., which solidified

to crystals of 2-phenyldihydroglyoxaline, m. p. 101° (6·1 g.; 42%). The product was characterised by preparing the derivatives mentioned in the Table (No. 6). (2) Ammonia was evolved when phenyl cyanide (5·15 g.), ethylenediammonium dichloride (3·35 g.; 0·5 mol.), and ethylenediamine (1·5 g.; 0·5 mol.) were heated under reflux for 2·5 hours in a bath at 200°. The product was shaken with water, unchanged phenyl cyanide (3·3 g.; 64%) was collected in benzene, and the amidine, liberated by adding 5N-sodium hydroxide, was purified by distillation, and had m. p. and mixed m. p. 101°. Yield, 2·7 g.; 36%.

2-(4′-*Methylsulphonylphenyl*)*dihydroglyoxaline*.—(1) *p*-Cyanophenyl methyl sulphone (9·05 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (11·6 g.; 1 mol.) were heated at 200° for ½ hour, ammonia being evolved. The product was crystallised from water (100 c.c.) giving 17·7 g. (89%) of 2-(4′-*methylsulphonylphenyl*)*dihydroglyoxalinium toluene*-p-*sulphonate*, m. p. 265°, which afforded 2-(4′-*methylsulphonylphenyl*)*dihydroglyoxaline*, m. p. 213·5°, with aqueous alkali (see No. 13 in Table). When the reaction mixture was heated at 125° for an hour the product consisted of unchanged cyanide (26%) and the dihydroglyoxalinium toluene-*p*-sulphonate (74%), which were separated by extracting the cyanide with acetone. (2) The product obtained by heating the cyanide (9·05 g.) and ethylenediammonium bistoluene-*p*-sulphonate (20·2 g.; 1 mol.) at 270° for 1½ hours was recrystallised from water and afforded 17·1 g. (86%) of 2-(4′-methylsulphonylphenyl)dihydroglyoxalinium toluene-*p*-sulphonate, m. p. 265°. (3) A mixture of *p*-cyanophenyl methyl sulphone (9·05 g.), ethylenediammonium dichloride (3·35 g.; 0·5 mol.), and ethylenediamine (1·5 g.; 0·5 mol.) was heated at 200° for ½ hour and the product crystallised from aqueous 80% *iso*propanol or from methanol giving 12·0 g. (92%) of 2-(4′-*methylsulphonylphenyl*)*dihydroglyoxalinium chloride*, m. p. 337° (decomp.) (see Note 13). (4) The cyanide (4·5 g.) and ethylenediamine (1·75 g.; 1·2 mols.) were heated at 205—210° for 1½ hour under reflux and the product crystallised from *iso*propanol. The yield of 2-(4′-methylsulphonylphenyl)dihydroglyoxaline, m. p. 213·5°, was 5 g. (90%).

Dihydroglyoxalines from Mixed Imides.

2-*Phenyldihydroglyoxaline from* N-*Benzoylbenzenesulphonmethylamide*.—A mixture of *N*-benzoylbenzenesulphonmethylamide (13·75 g.) and ethylenediammonium dichloride (3·35 g.; 0·5 mol.) was heated to *ca.* 225°, then cooled to 210° during the vigorous evolution of hydrogen chloride, and finally maintained at 225° for 15 minutes. The product was made strongly alkaline with aqueous sodium hydroxide and the basic oil (7·1 g.) was collected in chloroform. Sulphamic acid was added to a solution of this oil in methanol until the solution was just acid to Congo-red; the colourless rhombic plates (5·0 g.) which separated on keeping proved to be 2-*phenyldihydroglyoxalinium sulphamate*, m. p. 220° (decomp.) (Found: N, 17·1. $C_9H_{19}O_3N_3S$ requires N, 17·3%). 2-Phenyldihydroglyoxaline, m. p. and mixed m. p. 101°, was liberated from this salt and was converted into the picrate, benzenesulphonate, and toluene-*p*-sulphonate (see Table No. 6). When the filtrate from the first crop of sulphamate was diluted with a little ether it afforded 1·1 g. of sulphamate, m. p. 210—212° raised to 220° (decomp.) on recrystallisation from methanol. The yield of pure sulphamate was 5·6 g. (46%). The crystals (5·15 g.; 42%), m. p. 157—158°, which separated when the mother-liquor from the sulphamate was diluted with ether and kept for 12 hours were recrystallised from *iso*propanol and gave NN′-*dimethylbenzamidinium sulphamate*, m. p. 159° (Found: N, 17·1. $C_9H_{15}O_3N_3S$ requires N, 17·1%). This salt was converted successively into *NN*′-dimethylbenzamidine, m. p. and mixed m. p. 80—81°, and its picrate, m. p. and mixed m. p. 172·5°.

NN′-*Dibenzoyl*-1 : 2-*bistoluene*-p-*sulphonamidoethane*.—1 : 2-Bistoluene-*p*-sulphonamidoethane, m. p. 163°, was prepared from ethylenediamine, toluene-*p*-sulphonyl chloride (2 mols.), and aqueous sodium hydroxide (2 mols.) as described by Howard and Marckwald (*loc. cit.*), who record m. p. 159·5—160·5°. When a solution of potassium hydroxide (9 g.; 1 mol.) in methanol (50 c.c.) was added to a clear solution of potassium hydroxide (9 g.) and the bis-sulphonamide (53 g.) in methanol (150 c.c.), the dipotassium salt began to separate. After addition of *iso*propanol (100 c.c.), the salt (65 g.) was collected, dried, and suspended in benzene (250 c.c.). When benzoyl chloride (40·5 g.; 2 mols.) was added there was a vigorous reaction and, after 15 minutes' boiling, the solid was collected, washed with methanol and then with water to remove potassium chloride. The crude product (58 g.; 70%), m. p. 192—194°, was recrystallised from 2-ethoxyethanol giving colourless needles of NN′-*dibenzoyl*-1 : 2-*bistoluene*-p-*sulphonamidoethane*, m. p. 195° (Found: N, 4·9. $C_{30}H_{28}O_6N_2S$ requires N, 4·9%). A mixture of this compound (14·4 g.) with ammonium toluene-*p*-sulphonate (9·45 g.; 2 mols.) was heated at 200—205° for 1 hour, a liquid refluxing during the final stages. The mixture was shaken with water (100 c.c.) and benzene, which collected phenyl cyanide, b. p. 76—77°/14 mm. (1·5 g.; 58·5%). The aqueous solution was mixed with 5N-sodium hydroxide (50 c.c.) and extracted with chloroform giving 3·4 g. (93%) of 2-phenyldihydroglyoxaline, which had m. p. 101° after crystallisation from benzene–light petroleum. The product did not depress the m. p. of an authentic specimen of 2-phenyldihydroglyoxaline and its identity was confirmed by preparing the picrate, m. p. and mixed m. p. 242°.

Demethylation of 2-p-*Anisyldihydroglyoxaline*.—A mixture of 2-*p*-anisyldihydroglyoxaline (5·9 g.) and 45% aqueous hydrobromic acid (60 g.; 10 mols.) was boiled for 7 hours, distilled to remove most of the acid, and an aqueous solution of the residue was made alkaline with sodium carbonate. The solid was collected, washed, dried (5·1 g.; 94·5%), and recrystallised from methanol or water, giving colourless needles which slowly became yellow on exposure to air. 2-p-*Hydroxyphenyldihydroglyoxaline* begins to char at 290° and has m. p. *ca.* 300° (Found: N, 17·1. $C_9H_{10}ON_2$ requires N, 17·3%). The *picrate* crystallised from methanol in large rhombs, m. p. 223° (Found: N, 18·0. $C_{15}H_{13}O_8N_5$ requires N, 17·9%), and the *hydrochloride* separated from *iso*propanol in prisms, m. p. 246—247° (Found: N, 13·8, 14·0. $C_9H_{11}ON_2Cl$ requires N, 14·1%).

Amidines from 2-*Diethylaminoethylamine.*

N-2-*Diethylaminoethylbenzamidine*.*—Ammonium toluene-*p*-sulphonate (8·75 g.; 1 mol.) and 2-diethylaminoethylamine (5·8 g.) (Bloom, Breslow, and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 539)

* Experiments by Mr. J. Miller.

were kept at 100° until ammonia ceased to be evolved; phenyl cyanide (5·2 g.; 1 mol.) was then added and the mixture heated at 200° for an hour. The product was shaken with water and unchanged phenyl cyanide removed in chloroform. The aqueous solution was made strongly alkaline, and the oil which separated was collected in chloroform. Distillation of the extract afforded a fraction (4·4 g.; 40%) of crude N-2-*diethylaminoethylbenzamidine*, b. p. 152—156°/0·5 mm. (Found: equiv., by titration, 115. $C_{13}H_{21}N_3$ requires equiv., 109·5). The *dipicrate* had m. p. 134—135° (Found: N, 18·8. $C_{25}H_{27}O_{14}N_9$ requires N, 18·6%), and the *dihydrochloride trihydrate* consisted of deliquescent crystals with no definite m. p. (Found: N, 12·0, 12·1; Cl, 20·8. $C_{13}H_{23}N_3Cl_2,3H_2O$ requires N, 12·1; Cl, 20·5%).

N-2-*Diethylaminoethyl*-p-*amidinophenyl Methyl Sulphone*.*—Equimolecular proportions of ammonium toluene-*p*-sulphonate, 2-diethylaminoethylamine, and *p*-cyanophenyl methyl sulphone, brought into reaction as described in the preceding section, afforded 55% of recovered cyanide and 20% of crude *N*-2-diethylaminoethyl-*p*-amidinophenyl methyl sulphone as a light brown oil. The *dipicrate* had m. p. 202° (Found: N, 16·5, 16·4. $C_{26}H_{29}O_{15}N_9S$ requires N, 16·7%), and the *dihydrochloride dihydrate* decomposed at 100° (Found: N, 10·4. $C_{14}H_{25}O_2N_3Cl_2S,2H_2O$ requires N, 10·35%).

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97. *Tetra-aryl-phosphonium, -arsonium, and -stibonium Salts. Part III. The Synthesis and Properties of Tetra-aryl-arsonium Salts having Four Dissimilar Aryl Groups.*

By FREDERICK G. MANN and JAMES WATSON.

The synthesis of a number of quaternary arsonium iodides having four unlike aryl groups is described. Such salts should be incapable of dissociation to a tertiary arsine and an iodohydrocarbon, and consequently should be resolvable into enantiomorphs having high optical stability. All attempts to resolve these salts have failed, however. This is attributed solely to their physical properties, which make the necessary manipulative processes exceedingly difficult.

IT has been suggested that the considerable difficulty attending the isolation of an asymmetric quaternary arsonium salt in optically stable forms is due to the fact that such salts in solution may form a "dissociation equilibrium" of the type $[abcdAs]X \rightleftarrows abcAs + dX$ (Burrows and Turner, *J.*, 1921, **119**, 426; Holliman and Mann, *J.*, 1943, 551; Mann, *J.*, 1945, 68). This explanation received strong support from the resolution into optically stable forms of 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium bromide, a salt which possessed considerable chemical stability and therefore would not undergo the above type of dissociation (Holliman and Mann, *loc. cit.*). Further confirmation could be obtained by the preparation and optical resolution of an arsonium salt, [abcdAs]X, in which a, b, c, and d were unlike *aryl* groups: dissociation of such a compound in solution would be exceedingly improbable, and the compound when resolved should possess high optical stability. It should be noted that the configuration of such salts is beyond reasonable doubt, as Mooney (*J. Amer. Chem. Soc.*, 1940, **62**, 2955) has shown by *X*-ray analysis that tetraphenylarsonium iodide has a tetrahedral cation. The chief object of this paper is to describe the synthesis of such salts: a brief account of their attempted resolution is also included.

Only two reactions are known for the preparation of tetra-arylarsonium salts. Blicke and Monroe (*J. Amer. Chem. Soc.*, 1935, **57**, 720) have shown that triphenylarsine oxide, when treated in turn with phenylmagnesium bromide and hydrobromic acid, yields tetraphenylarsonium bromide, but this reaction appears to have limited application for the synthesis of tetra-arylarsonium salts (Blicke and Cataline, *ibid.*, 1938, **60**, 423) and therefore to be unsuitable for the preparation of salts required in the present work. Chatt and Mann (*J.*, 1940, 1192) have shown, however, that triphenylarsine reacts with bromobenzene in the presence of aluminium chloride to form tetraphenylarsonium bromide: the mechanism of this reaction has been elucidated by Lyon and Mann (*J.*, 1942, 666), who showed that unlike aryl groups could thus be introduced into the arsonium ion, as, for instance, to form triphenyl-*p*-tolylarsonium and diphenyldi-*p*-tolylarsonium salts. We find that arsonium salts containing four dissimilar aryl groups can be prepared by Chatt and Mann's reaction provided the groups be inserted in the appropriate order, and that pure aluminium chloride be used in the final reaction.

This synthesis clearly entails the previous preparation of tertiary arsines, abcAs, having three unlike aryl groups: no such arsines had been recorded but they can readily be prepared by the action of a suitable Grignard reagent on the corresponding diarylmonochloroarsines of type abAsCl.

Symmetric diarylmonochloroarsines, *e.g.*, diphenylchloroarsine, $AsPh_2Cl$, are frequently prepared by the action of the requisite diarylmercury on the monoaryldichloroarsine: $AsPhCl_2 + Ph_2Hg = AsPh_2Cl + HgPhCl$. We find that this method cannot safely be used for the preparation of diarylmonochloroarsines having two unlike aryl radicals, because dismutation so readily occurs; for instance, a mixture of diphenylmercury and *p*-tolyldichloroarsine, heated at 220—230° for 5 hours, furnished mainly di-*p*-tolylmonochloroarsine.

In our preliminary experiments, therefore, we utilised a modified Bart's reaction, phenylarsine oxide being treated with sodium *p*-tolyldiazoate in sodium hydroxide solution to form phenyl-*p*-tolylarsinic acid (I) (cf. Kamai, *Trans. Kirov Inst. Chem. Tech. Kazan*, 1935, **3**, 49), which on reduction with sulphur dioxide and hydrochloric acid gave phenyl-*p*-tolylchloroarsine (II), the identity of which was thus beyond doubt. This arsine, when treated with *p*-chlorophenylmagnesium iodide, then furnished the viscous liquid *phenyl*-p-*tolyl*-p-*chlorophenylarsine* (III).

$$AsPhO \xrightarrow{p\text{-}C_6H_4Me\cdot N_2OH} \underset{(I.)}{Ph(p\text{-}C_6H_4Me)AsO(OH)} \xrightarrow{SO_2/HCl} \underset{(II.)}{Ph(p\text{-}C_6H_4Me)AsCl} \xrightarrow{p\text{-}C_6H_4Cl\cdot MgI}$$

$$\underset{(III.)}{Ph(p\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As} \xrightarrow[+\ AlCl_3]{m\text{-}C_6H_4MeBr} \underset{(IV.)}{[Ph(p\text{-}C_6H_4Me)(m\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As]I}$$

The arsine (III), when heated with *m*-bromotoluene and aluminium chloride followed by aqueous extraction and treatment with potassium iodide, yielded the colourless crystalline *phenyl*-p-*tolyl*-m-*tolyl*-p-*chlorophenylarsonium iodide* (IV), the first salt of the required type to be isolated. This salt was converted by the usual methods into the d-*bromocamphorsulphonate* and the *d*-camphornitronate: both salts formed friable, slightly hygroscopic glasses which could not be recrystallised, and fractional precipitation of the sulphonate gave no evidence of optical resolution. It was thought that this failure might possibly be due to isomerisation of the *m*-bromotoluene when heated with the aluminium chloride at 180—190° to prepare the arsonium salt (IV), whereby the two tolyl groups might become identical. No indication of such isomerisation had ever been obtained, however, and its improbability was shown by the fact that a mixture of triphenylarsine and aluminium chloride, when heated with *m*-bromotoluene and *p*-bromotoluene respectively and subsequently treated in each case with potassium iodide, gave the two distinct salts, *triphenyl*-m-*tolylarsonium iodide* and triphenyl-*p*-tolylarsonium iodide.

The arsine (III) was then heated with *p*-bromoethylbenzene and aluminium chloride, and thus converted into phenyl-*p*-tolyl-*p*-ethylphenyl-*p*-chlorophenylarsonium iodide. Similarly, the chloro-arsine (II) was treated with *p*-ethylphenylmagnesium bromide to form *phenyl*-p-*tolyl*-p-*ethylphenylarsine*, which when heated with *m*-bromotoluene and aluminium chloride, followed by precipitation of the product with potassium thiocyanate, furnished phenyl-*p*-tolyl-*m*-tolyl-*p*-ethylphenylarsonium thiocyanate. Neither of these arsonium salts, however, could be obtained crystalline.

It is noteworthy that the introduction of *p*-alkyl substituents larger than the ethyl group into such salts is apparently not practicable. *p*-Bromo-*n*-propylbenzene would not react with triarylarsines in the presence of aluminium chloride: even had it so reacted, the constitution of the product would have been uncertain, because the *n*-propyl group might well have isomerised under the influence of the aluminium chloride.

Heavier aryl groups were now employed in the hope that their presence would induce readier crystallisation. For this purpose, phenylarsine oxide was treated with sodium *p*-phenylyldiazoate to obtain phenyl-*p*-phenylylarsinic acid (V), which Blicke and Smith (*J. Amer. Chem. Soc.*, 1929, **51**, 3481) had formerly made by the action of *p*-phenylylmagnesium bromide on phenylarsine oxide, followed by treatment first with chlorine and then with sodium hydroxide. The acid (V) was reduced to phenyl-*p*-phenylylchloroarsine (VI), which was then

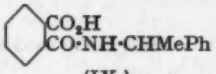
$$\underset{(V.)}{Ph(p\text{-}C_6H_4Ph)AsO(OH)} \longrightarrow \underset{(VI.)}{Ph(p\text{-}C_6H_4Ph)AsCl} \longrightarrow \underset{(VII.)}{Ph(p\text{-}C_6H_4Ph)(p\text{-}C_6H_4Cl)As} \longrightarrow \underset{(VIII.)}{[Ph(p\text{-}C_6H_4Me)(p\text{-}C_6H_4Ph)(p\text{-}C_6H_4Cl)As]I}$$

converted by *p*-chlorophenylmagnesium iodide into *phenyl*-p-*phenylyl*-p-*chlorophenylarsine* (VII). The latter, when heated with *p*-bromotoluene and aluminium chloride, furnished after the usual extraction *phenyl*-p-*tolyl*-p-*phenylyl*-p-*chlorophenylarsonium iodide* (VIII). This salt was then converted into the corresponding *d*-camphorsulphonate and d-*bromocamphorsulphonate*, but both salts could be isolated only as the usual friable, unrecrystallisable glasses. The arsine (VII) was also converted by the aluminium chloride reaction into *phenyl*-m-*tolyl*-

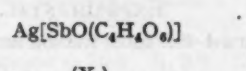
and *phenyl*-p-*ethylphenyl*-p-*phenylyl*-p-*chlorophenylarsonium iodide*, but neither salt could be readily recrystallised.

The above results showed clearly that the chief obstacle to success was the physical nature of these asymmetric arsonium salts. Two further steps were therefore taken in the hope of obtaining salts which would crystallise more readily and thus be physically better defined. First, salts were prepared in which three of the phenyl groups carried *para*-substituents, two of which were chloro- and bromo-groups, since the presence of *p*-halogenophenyl groups appeared to promote crystallisation. Secondly, a much wider variety of optically active acids was employed in the resolution experiments. Three of these acids require brief comment, as their use in optical resolution experiments has not apparently been previously recorded.

When equimolecular quantities of phthalic anhydride and *l*-α-phenylethylamine were boiled in ethereal solution, l-N-α-*phenylethylphthalamic acid* (IX) was obtained: this acid had $[M]_D$ 130° in ethyl-alcoholic solution, and gave a *silver* salt, which, being soluble in warm aqueous alcohol, could in turn readily be converted into the arsonium salts of the acid. It is noteworthy that the *l*-acid (IX) had m. p. 133°, whereas the *dl*-acid had m. p. 181°.



(IX.)



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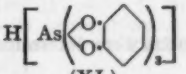


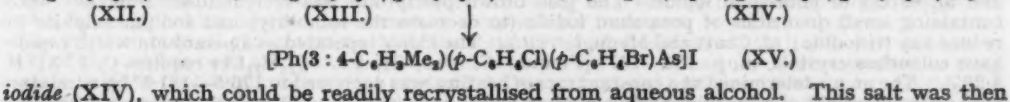
(XI.)

Secondly, Brinnard, Dyke, Jones, and Jones (*J.*, 1932, 1815) have shown that a number of quaternary phosphonium, arsonium, and stibonium halides react with silver *d*-antimonyl tartrate (X) to give well-crystallised salts freely soluble in water. The use of this complex optically active radical in our work therefore appeared very promising, because it might again induce ready crystallisation, and moreover water, instead of organic solvents, could now be used.

Thirdly, Rosenheim and Plato (*Ber.*, 1925, **58**, 2000) have shown that tricatechylarsenic acid (XI), originally prepared by Weinland and Heinzler (*Ber.*, 1919, **52**, 1316), can be readily resolved with cinchonine. The *l*-barium salt of this acid is soluble in water, has a high rotation, $[M]_D$ −2330°, and has reasonable optical stability in the absence of acids. By double decomposition with an arsonium sulphate, therefore, the quaternaryarsonium *l*-tricatechylarsenate could be obtained for resolution purposes.

We have also employed *l*-menthoxyacetic acid, derivatives of which Read and Grubb (*J. Soc. Chem. Ind.*, 1932, **51**, 330T) have successfully employed for optical resolutions.

We have therefore reduced phenyl-*p*-bromophenylarsinic acid to the crystalline *phenyl*-p-*bromophenylchloroarsine* (XII), and converted this by means of *p*-chlorophenylmagnesium iodide into *phenyl*-p-*chlorophenyl*-p-*bromophenylarsine* (XIII). This arsine was then converted by the aluminium chloride reaction into *phenyl*-p-*tolyl*-p-*chlorophenyl*-p-*bromophenylarsonium*



iodide (XIV), which could be readily recrystallised from aqueous alcohol. This salt was then converted by the usual methods into the d-*bromocamphorsulphonate*, the *d*-camphornitronate, and the *l*-*N*-α-phenylethylphthalamate, but these salts formed only friable glasses, and the *l*-menthoxyacetate was obtained only as a viscous oil. The d-*antimonyl tartrate* was, however, obtained crystalline, but after it had been repeatedly recrystallised from water, treatment with potassium iodide furnished the inactive iodide (XIV).

Finally, the arsine (XIII) was heated with aluminium chloride and 4-bromo-*o*-xylene, whereby *phenyl*-4-o-*xylyl*-p-*chlorophenyl*-p-*bromophenylarsonium iodide* (XV) was ultimately isolated. This iodide was converted into the *d*-bromocamphorsulphonate, the *l*-menthoxyacetate, the l-N-α-*phenylethylphthalamate*, and the d-*hydrogen tartrate*, but none of these salts could be recrystallised. The d-*antimonyl tartrate* was obtained in the crystalline condition, but recrystallisation proved unsatisfactory. Finally, the l-*tricatechylarsenate* was obtained as a white solid, but many attempts at fractional crystallisation or precipitation failed to give any trustworthy evidence of optical resolution.

This repeated failure to resolve so wide a variety of tetra-arylarsonium salts immediately raises the question whether the " dissociation-equilibrium " theory is an incomplete or inaccurate explanation of the prime difficulty involved, or whether the failure is due solely to the physical properties of these tetra-aryl salts. We incline strongly to the latter view. It is

noteworthy that tetraphenyl- and tetra-*p*-tolyl-arsonium iodides are highly crystalline salts that can be readily recrystallised (Chatt and Mann; Lyon and Mann, *locc. cit.*): this is to be expected, since the large but symmetric cation will pack conveniently into the crystal lattice. Our tetra-arylarsonium iodides having four unlike aryl groups usually crystallise with reluctance, whilst the corresponding salts with optically active acid radicals almost invariably form apparently amorphous glasses. This is also to be expected: the very large and now asymmetric cation would clearly not pack readily into the crystal lattice even in the iodides, but when the cation is also accompanied by an asymmetric anion, crystallisation appears to be almost completely inhibited, with the consequent formation of the familiar amorphous glasses. The fact that these glasses when pulverised are also slightly hygroscopic and therefore become sticky on exposure to air makes the necessary experimental manipulation even more difficult. It would appear that in these quaternary arsonium salts, the constitutional factor which would inhibit dissociation and thus give optical stability, namely, the presence of four unlike aryl groups, simultaneously makes the physical process of optical resolution almost impossible to achieve.

Experimental.

All rotations were determined in a 4-dm. tube, the sodium-D line ($\lambda = 5893$) being used as the source of light.

The aluminium chloride was always freshly prepared by the action of dry hydrogen chloride on heated aluminium, and then finely powdered: immediately before use it was confined in a desiccator over sodium hydroxide, as free hydrogen chloride can have a markedly harmful effect on the arsonium salt formation stage of our syntheses.

p-*Bromoethylbenzene*. *p*-Bromoacetophenone was prepared by the action of acetic anhydride on bromobenzene in the presence of aluminium chloride (Adams and Noller, *Org. Synth.*, **5**, 17), and then converted by a Clemmensen reduction into *p*-bromoethylbenzene.

p-*Bromo*-n-*propylbenzene*. *p*-Bromopropiophenone was prepared similarly by using propionic anhydride and obtained in 78% yield as colourless crystals, m. p. 47°, b. p. 138—140°/18·5 mm. For reduction, zinc (210 g.) was amalgamated by 5 minutes' immersion in water (250 c.c.) containing concentrated hydrochloric acid (10 c.c.) and mercuric chloride (16 g.). The solution was then decanted, and the zinc covered with concentrated hydrochloric acid (225 c.c.) diluted with water (175 c.c.). The bromo-ketone (115 g.) was added, and the mixture refluxed for 10 hours, hydrochloric acid (*ca.* 30 c.c.) being added at hourly intervals. After 14 hours' further refluxing, the mixture was distilled in steam, and the *p*-bromo-*n*-propylbenzene was extracted from the distillate with benzene, dried, and distilled; colourless liquid, b. p. 223—226°; 46 g. (45%). Meyer (*J. pr. Chem.*, 1886, **34**, 101) prepared this compound, b. p. 220°, by bromination of *n*-propylbenzene, and Copenhaver, Roy, and Marvel (*J. Amer. Chem. Soc.*, 1935, **57**, 1313) by the interaction of *p*-bromophenylmagnesium bromide and *n*-propyl *p*-toluenesulphonate.

Triphenyl-m-*tolylarsonium iodide*. This preparation was undertaken to determine whether any indication of isomerisation of tolyl groups during the aluminium chloride reaction could be observed. Its description serves essentially for all similar preparations subsequently cited. Triphenylarsine (3 g.), aluminium chloride (1·35 g., 1 mol.), and *m*-bromotoluene (3·3 g., 2 mols.) were heated together at 180—190° for 1·25 hours, the hot melt being then slightly dark but transparent. The cold product was extracted with much boiling water, and the cold filtrate treated in turn with 2 or 3 drops of acetic acid and an excess of potassium iodide. The pale brown precipitate was recrystallised from hot water containing small quantities of potassium iodide (to decrease the solubility) and sodium sulphite (to reduce any tri-iodide; cf. Chatt and Mann, *loc. cit.*). The *iodide* separated as an emulsion which rapidly gave colourless crystals, m. p. 185—187° (Found: C, 57·4; H, 4·5. $C_{31}H_{32}IAs$ requires C, 57·3; H, 4·2%). The m. p., determined at a constant rate of heating, was depressed to 176·5—181·5° by admixture with an equal weight of triphenyl-*p*-tolylarsonium iodide of m. p. 178—179°; since, moreover, the latter iodide separates as a monohydrate (Lyon and Mann, *loc. cit.*), the two iodides were clearly distinct.

Triphenyl-p-*ethylphenylarsonium iodide*. This preparation was carried out to determine whether *p*-bromoethylbenzene would react with triarylarsines under the influence of aluminium chloride. Triphenylarsine (3 g.), aluminium chloride (1·35 g., 1 mol.), and *p*-bromoethylbenzene (2·4 c.c.) were heated together at 180—190° for 1·5 hours. The usual extraction and aqueous recrystallisation ultimately yielded the *monohydrated iodide* as colourless crystals, whose m. p. varied greatly with the speed of heating (Found: C, 56·5; H, 4·9. $C_{34}H_{34}IAs,H_2O$ requires C, 56·1; H, 4·7%).

Phenyl-p-*tolylarsinic acid* (I). The yield of diarylarsinic acids prepared by the Bart reaction depends largely on the pH at which the reaction is carried out. Many experiments showed that the following conditions afforded the highest yield. A solution of *p*-toluidine (10·7 g.) in water (250 c.c.) containing concentrated hydrochloric acid (25·5 c.c.) was diazotised by addition of a solution of sodium nitrite (7·2 g., 1·04 mols.) in water (25 c.c.). The stirred solution was maintained below 5° whilst a solution of phenylarsine oxide (17 g., 1 mol.) in N-sodium hydroxide (180 c.c.) was added dropwise during 1·5 hours, followed by the similar addition of N-sodium hydroxide (100 c.c.) during 20 minutes. Effervescence occurred during the later stages of this treatment. After 12 hours, the solution was filtered to remove red tarry matter and then made just acid to Congo-red. A red gum separated first, followed by colourless crystals. The mixture was boiled (whereby only the crystals dissolved) and filtered, and the residual molten red gum extracted again with boiling water. The two filtrates when chilled deposited the arsinic acid (I), m.p. 150—152° (Found: C, 56·0; H, 5·2. Calc. for $C_{13}H_{13}O_2As$: C, 56·5; H, 4·75%); 11 g. (40%). A sample after recrystallisation from water had m. p. 156—157°; Kamai (*loc. cit.*) gives m. p. 159—160°. When the quantities used above were increased *ca.* tenfold, the yield fell to 32%.

Phenyl-p-*tolylchloroarsine* (II). A solution of the above acid (8·1 g.) in a mixture of methanol (40 c.c.) and concentrated hydrochloric acid (16 c.c.) containing a crystal of potassium iodide was heated on a steam-bath whilst sulphur dioxide was passed through for 2 hours. The mixture was cooled, diluted with water (150 c.c.), and the yellow oil extracted with light petrol, dried, and distilled after removal of the solvent. The *chloro-arsine* was obtained as a pale yellow oil, b. p. 175—180°/0·05 mm. (Found: Cl, 12·7. $C_{13}H_{12}ClAs$ requires Cl, 12·7%); 6·2 g. (76%).

Phenyl-p-*tolyl*-p-*chlorophenylarsine* (III). A solution of the chloro-arsine (II) (12 g.) in ether (40 c.c.) was added during 45 minutes to an ice-cold, stirred Grignard reagent which had been prepared by the interaction of magnesium (1·57 g., 1·5 atoms) and *p*-chloroiodobenzene (15·4 g., 1·5 mols.) in ether (40 c.c.) to which a small iodine crystal had been added. The mixture was then refluxed for two hours, cooled, and hydrolysed by addition of a solution of ammonium chloride (12 g.) in water (50 c.c.). The ethereal layer when separated, dried, and distilled ultimately gave the *arsine* (III) as a colourless viscous liquid, b. p. 208—210°/2 mm., which could not be obtained crystalline (Found: C, 64·4; H, 4·3. $C_{19}H_{16}ClAs$ requires C, 64·3; H, 4·5%).

For characterisation, a chilled, agitated solution of the arsine (2·73 g.) in acetic acid (10 c.c.) was treated dropwise with bromine (1·25 g., 1 mol.), instant decolorisation occurring. The solution was then poured into 30% aqueous sodium hydroxide (125 c.c.), the mixture refluxed for 1 hour, and the oily precipitate extracted with chloroform. The extract when dried, filtered, and evaporated, afforded the *arsine oxide* as a viscous residue which rapidly solidified and after recrystallisation (*cyclo*hexane) was obtained as very deliquescent, colourless, feathery crystals, m. p. 130° (Found: C, 61·7; H, 4·3. $C_{19}H_{16}OClAs$ requires C, 61·5; H, 4·35%). An alcoholic solution of this oxide, treated with picric acid, gave the *arsine hydroxy-picrate*, greenish-yellow crystals from alcohol, m. p. 174° (Found: C, 50·7; H, 3·2; N, 7·4. $C_{31}H_{19}O_8N_3ClAs$ requires C, 50·0; H, 3·2; N, 7·0%).

It was thought that the tertiary arsine (III) might be better prepared if the aryl groups were introduced in the order: $PhAsO \longrightarrow Ph(p\text{-}C_6H_4Cl)AsO(OH) \longrightarrow Ph(p\text{-}C_6H_4Cl)AsCl \longrightarrow Ph(p\text{-}C_6H_4Me)(p\text{-}C_6H_4Cl)As$. *Phenyl*-p-*chlorophenylarsinic acid* was therefore prepared similarly to (I), a solution obtained from *p*-chloroaniline (12·75 g.), in water (140 c.c.) and concentrated hydrochloric acid (35 c.c.), being first diazotised by addition of a solution of sodium nitrite (7 g.) in water (50 c.c.), and then treated at 5° dropwise with a solution of phenylarsine oxide (17 g., 1 mol.) in water (300 c.c.) containing sodium hydroxide (16 g.). The cold mixture was stirred for 3 hours, set aside for 2 days, filtered, and made just acid to Congo-red. The precipitated arsinic acid (8·2 g., 28%), after two recrystallisations from water, was obtained as colourless needles, m. p. 162—163° (Found: C, 49·2; H, 3·4; Cl, 12·2. $C_{19}H_{16}O_2ClAs$ requires C, 48·6; H, 3·4; Cl, 12·0%). The conversion of this acid into the corresponding chloro-arsine proved unsatisfactory, however, and this alternative route to the arsine (III) was therefore abandoned.

Phenyl-p-*tolyl*-m-*tolyl*-p-*chlorophenylarsonium iodide* (IV). The arsine (III) (16·6 g.), *m*-bromo toluene (11·4 c.c., 2 mols.), and aluminium chloride (6·2 g.) were heated at 180—190° for 2 hours. The usual extraction, followed by potassium iodide treatment, precipitated the *iodide* as an oil which crystallised only after several days: recrystallisation from water was equally slow, and final purification was achieved by cautious addition of ether to a cold alcoholic solution of the iodide. The latter was thus obtained as colourless crystals, m. p. 148—151° (Found: C, 54·2; H, 4·3. $C_{26}H_{23}ClIAs$ requires C, 54·5; H, 4·05%).

The arsonium *d*-bromocamphorsulphonate was prepared by interaction of the iodide and silver *d*-bromocamphorsulphonate (1 mol.) in rectified spirit. The mixture, when boiled for 10 minutes, filtered, and evaporated, afforded the sulphonate as a viscous oil, which was very soluble in cold methyl and ethyl alcohols, acetone, acetic acid and dioxan, and insoluble in ether, *cyclo*hexane and petrol. It dissolved in hot benzene and hot ethyl carbonate, but separated as an oil as each solution cooled. Repeated extraction with cold petrol, however, ultimately gave the residual *monohydrated* sulphonate as a very hygroscopic, brittle, white solid (Found: C, 55·9; H, 5·6. $C_{36}H_{37}O_4ClBrSAs,H_2O$ requires C, 55·8; H, 5·1%), which, however, could not be recrystallised from pure or mixed solvents. A solution of the sulphonate in ethyl acetate was therefore cautiously treated with petrol (b. p. 40—60°) until about 50% of the salt has been precipitated as the usual syrup: the latter was collected, redissolved in ethyl acetate, and the fractional precipitation repeated. This process was performed four times, and the final oily precipitate then converted into the brittle solid by treatment with cold petrol. The solid sulphonate could not be converted into a picrate, and was therefore converted into the mercuritri-iodide: the latter, however, was inactive.

The arsonium *d*-camphornitronate was similarly prepared by the interaction of the iodide and silver *d*-camphornitronate in hot methyl-alcoholic solution, boiling being avoided to prevent possible decomposition. Filtration of the mixed solutions followed by evaporation in a vacuum gave the arsonium nitronate as a syrup which also formed a brittle hygroscopic glass on treatment with petrol, but could not be crystallised.

When the arsine (III) was heated with *p*-bromoethylbenzene (1·7 mols.) and aluminium chloride (1 mol.) at 180—190° for 1·5 hours, the usual treatment afforded ultimately a crystalline iodide which, however, on exposure to damp air rapidly formed a sticky semi-solid mass. This could not be recrystallised, and was not further investigated.

Phenyl-p-*tolyl*-p-*ethylphenylarsine*. This arsine was prepared by the interaction of a solution of phenyl-*p*-tolylchloroarsine (12 g.) in ether (40 c.c.) and a Grignard reagent prepared from *p*-bromoethylbenzene (12 g., 1·5 mols.) and magnesium (1·57 g., 1·5 atoms) in ether (40 c.c.). After the usual treatment, the *arsine* was isolated initially as a liquid, b. p. 196—198°/0·2 mm., which rapidly solidified, and after recrystallisation from alcohol formed colourless crystals, m. p. 73° (Found: C, 72·0; H, 5·9. $C_{21}H_{21}As$ requires C, 72·4; H, 6·0%). A solution of this arsine in acetic acid rapidly united with 1 equiv. of bromine: the resultant dibromide was hydrolysed by boiling with aqueous sodium hydroxide, and the arsine oxide extracted with chloroform. Removal of the solvent gave an oil which ultimately solidified, and on recrystallisation from *cyclo*hexane furnished the hygroscopic *diarsine oxide-dihydroxide*, $(C_{21}H_{21}AsOH)_2O$ (Found: C, 67·4; H, 5·8. $C_{42}H_{44}O_3As_2$ requires C, 67·5; H, 5·9%). This compound

in alcohol gave the *arsine hydroxy-picrate*, yellow needles from alcohol, m. p. 133° (Found: C, 54·5; H, 4·5; N, 7·4. $C_{27}H_{24}O_9N_3As$ requires C, 54·6; H, 4·1; N, 7·1%).

When phenyl-*p*-tolyl-*p*-ethylphenylarsine was heated with *m*-bromotoluene and aluminium chloride as usual, the ultimate aqueous extract gave solid precipitates with both potassium iodide and thiocyanate: neither precipitate could be recrystallised, however, and was not further investigated.

Phenyl-p-*phenylylarsinic acid* (V). *p*-Aminodiphenyl was prepared by nitration of diphenyl, followed by purification and reduction of the *p*-nitrodiphenyl (Morgan and Walls, *J. Soc. Chem. Ind.*, 1930, **49**, 15τ). Several experiments showed the following to give the highest yield of the arsinic acid. A solution of *p*-aminodiphenyl (16·9 g.) in hot water (500 c.c.) containing concentrated hydrochloric acid (25·5 c.c.) was cooled and stirred, so that the amine hydrochloride separated in fine crystals. Ice (200 g.) was added, and the mixture well stirred whilst a solution of sodium nitrite (7·2 g., 1 mol.) in water (25 c.c.) was slowly added. A solution of sodium hydroxide (7·2 g.) and phenylarsine oxide (17 g., 1 mol.) in water (180 c.c.) was then added dropwise during 1·5 hours to the stirred diazonium solution kept between 4° and 8°: each drop produced effervescence and a red precipitate. When the addition was complete, the solution was stirred for 1 hour longer, then diluted with a solution of sodium hydroxide (4 g.) in water (100 c.c.) and set aside for 12 hours. The filtered solution was then made just acid to Congo-red. The precipitated arsinic acid (7·3 g., 22%) was collected and recrystallised from alcohol (charcoal): the pure acid (4 g., 12%) had m. p. 221—225° (Found: C, 64·5; H, 4·7. Calc. for $C_{18}H_{15}O_3As$: C, 63·9; H, 4·5%). Blicke and Smith (*loc. cit.*) give m. p. 218—220°. When the above quantities were increased seven-fold, the yield was 14%.

Phenyl-*p*-phenylylchloroarsine (VI) was prepared from this acid by the usual hydrochloric acid–sulphur dioxide reduction at 100°; colourless needles from alcohol, m. p. 87—88°, b. p. 211—212°/0·4 mm.; yield, 87% (Found: C, 63·7; H, 4·5; Cl, 10·5. Calc. for $C_{18}H_{14}ClAs$: C, 63·5; H, 4·1; Cl, 10·4%). Blicke and Smith (*loc. cit.*) give m. p. 83—85°.

Phenyl-p-*phenylyl*-p-*chlorophenylarsine* (VII). A Grignard reagent prepared from *p*-chloroiodobenzene (29·5 g., 1·7 mols.) and magnesium (3 g., 1·7 atoms) in ether (100 c.c.) under a nitrogen atmosphere, was chilled to 0° and stirred whilst a solution of the chloro-arsine (VI) (25·3 g.) in benzene (90 c.c.) was slowly added. The mixture was refluxed for 2 hours, chilled, and hydrolysed with a solution of ammonium chloride (25 g.) in water (125 c.c.). The usual procedure then furnished the *arsine* (VII) as a clear yellow syrup, b. p. 279—290°/0·3 mm., which could not be induced to crystallise (Found: C, 69·05; H, 4·4; Cl, 9·3. $C_{24}H_{18}ClAs$ requires C, 69·15; H, 4·4; Cl, 8·5%); 28 g. (90%).

The *arsine oxide* was prepared by the usual bromine addition followed by hot alkaline hydrolysis; evaporation of the chloroform extract gave the oxide as an oil which solidified when extracted with cold petrol, and then, when recrystallised from ethyl acetate, formed colourless crystals, m. p. 163° (Found: C, 66·4; H, 4·2. $C_{24}H_{18}OClAs$ requires C, 66·6; H, 4·2%). This in turn furnished the *hydroxy-picrate*, greenish-yellow crystals, m. p. 146·5—148·5°, from alcohol (Found: C, 54·0; H, 3·5; Cl, 6·0. $C_{30}H_{21}O_9N_3ClAs$ requires C, 54·4; H, 3·2; Cl, 5·4%).

Phenyl-p-*tolyl*-p-*phenylyl*-p-*chlorophenylarsonium iodide* (VIII). A mixture of arsine (VII) (13·2 g.), *p*-bromotoluene (10·8 g., 2 mols.), and aluminium chloride (4·2 g.) was heated at 185—190° for 1·5 hours, cooled and twice extracted with 600 c.c. of boiling water. Potassium iodide, added to the cold, united, filtered extracts, precipitated the above *monohydrated arsonium iodide* (11·5 g., 56%), which was then recrystallised from a large volume of water containing a small amount of alcohol and a trace of sodium sulphite; colourless solid, m. p. indefinite 90—125° (efferv.) (Found: C, 57·0; H, 4·2. $C_{31}H_{28}ClIAs,H_2O$ requires C, 57·0; H, 4·2%).

The arsonium *d*-bromocamphorsulphonate, prepared in the usual way, was obtained after evaporation of its alcoholic solution in a desiccator as a syrup which was converted into a brittle solid by repeated extraction with cold petrol. Although this solid dissolved in many organic liquids, it could not be recrystallised and usually separated from these solutions as a viscous syrup. For purification, a sample was dissolved in alcohol, precipitated as a syrup by addition of petrol, and the syrup again extracted with cold petrol until the *dihydrate* became solid (Found: C, 57·7; H, 5·4. $C_{41}H_{39}O_4ClBrSAs,2H_2O$ requires C, 57·6; H, 5·1%).

A similar preparation of the *d*-camphorsulphonate gave a syrupy residue which ultimately formed a friable glass which could not be recrystallised.

Phenyl-m-*tolyl*-p-*phenylyl*-p-*chlorophenylarsonium iodide*. By using *m*-bromotoluene, this salt was prepared as the previous iodide, but in much smaller yield. A solution of the crude iodide in hot water containing a small proportion of alcohol on cooling gave an emulsion, which ultimately, on chilling and scratching, deposited the crystalline *iodide monohydrate*, melting indefinitely 75—135° (Found: C, 56·7; H, 4·2. $C_{31}H_{28}ClIAs,H_2O$ requires C, 57·0; H, 4·2%).

Phenyl-p-*ethylphenyl*-p-*phenylyl*-p-*chlorophenylarsonium iodide*. This salt was prepared by interaction of the above tertiary arsine (2·1 g.), *p*-bromoethylbenzene (1·6 g., 1·7 mols.), and aluminium chloride (0·7 g., 1 mol.) at 185—190° for 1·25 hours. The cold product was extracted six times with boiling water (300 c.c. in all), and the cold filtered extracts precipitated by potassium iodide. The *arsonium iodide monohydrate* was ultimately purified by slowly cooling a solution in hot water containing a small proportion of alcohol, potassium iodide, and sodium sulphite; the viscous syrup which initially separated crystallised after the solution had been kept at 0° for 12 hours (Found: C, 57·5; H, 4·5. $C_{33}H_{27}ClIAs,H_2O$ requires C, 57·6; H, 4·4%). The iodide has an indefinite m. p.

The preparation of certain optically active acids and their salts used in subsequent experiments is now described.

l-N-α-*Phenylethylphthalamic acid* (IX). A solution of *l*-α-phenylethylamine (5·4 g.) in ether (30 c.c.) was added rapidly to a solution of phthalic anhydride (6·6 g., 1 mol.) in boiling ether (200 c.c.), the mixture refluxed for 30 minutes, and cooled. The syrupy acid which had separated slowly recrystallised; after filtration, a second crop was obtained either by concentration or by careful addition of light petrol. The united crops were recrystallised from ether, and furnished the colourless *acid*, m. p. 134° (Found: C, 71·2; H, 5·3. $C_{16}H_{15}O_3N$ requires C, 71·3; H, 5·6%). A 0·394% alcoholic solution had α — 0·76°, [*M*] — 131°; a 0·559% solution had α — 1·08°, [*M*] — 130°.

The *dl*-acid was similarly prepared from the *dl*-amine, and recrystallised from acetone; colourless crystals, m. p. 181° (efferv.) (Found: C, 71·0; H, 5·7%).

Silver l-N-*α-phenylethylphthalamate*. The *l*-acid was dissolved in aqueous N-NaOH solution (1 equiv.), and a small excess of aqueous silver nitrate solution added. After 3 hours, the precipitated *silver* salt was collected and washed with water, alcohol, and ether; it formed a colourless powder (Found: Ag, 28·6. $C_{16}H_{14}O_3NAg$ requires Ag, 28·7%) moderately soluble in hot aqueous alcohol.

Silver d-*antimonyl tartrate monohydrate* (X). When solutions of tartar emetic (24·5 g.) in water (400 c.c.) and silver nitrate (15 g., 1·2 mols.) in water (100 c.c.) were mixed, the above monohydrate separated as hard white granules, which were collected, washed in turn with water, alcohol and ether, and dried. The salt is soluble in hot aqueous alcohol.

Silver l-*menthoxyacetate*. *l*-Menthoxyacetic acid was prepared by the method of Leffler and Calkins (*Org. Synth.*, 1943, **23**, 52), but although it was thrice distilled (b. p. 188—190°/17 mm., 119—122°/0·05 mm.), it could not be induced to crystallise. It was therefore dissolved in aqueous N-sodium hydroxide solution (1 equiv.), and silver nitrate (1 mol.) in aqueous solution added; the *silver* salt was precipitated as a white powder, which was collected, washed with water, and dried (Found: Ag, 33·5. $C_{12}H_{21}O_3Ag$ requires Ag, 33·6%). This salt is soluble in chloroform, slightly soluble in water, and almost insoluble in alcohol, acetone or methanol: boiling alcohol slowly decomposes it.

Barium l-*tricatechylarsenate*. (i) Tricatechylarsenic acid (XI) was prepared by adding catechol (100 g.) to a solution of arsenic acid (40 g.) in hot water (100 c.c.), boiling the mixture for 1—2 minutes, and then allowing it to cool. Crystallisation of the required acid was initially slow, but became rapid later. In subsequent preparations, seeding the solution caused crystallisation. The monohydrated acid was collected, washed with a small volume of water, and dried (cf. Weinland and Heinzler, *loc. cit.*). (ii) The arsenic acid (48 g.) was added to a solution of cinchonine (34 g., 1 mol.) in boiling alcohol (1100 c.c.), and the solution immediately filtered through a preheated filter. On cooling, colourless crystals of the cinchonine *l*-tricatechylarsenate (33 g.) rapidly separated; a 0·304% acetone solution had α −3·15°, $[\alpha]$ −259° (cf. Rosenheim and Plato, *loc cit.*). (iii) This *l*-anion is optically stable only in alkaline solution, and the following preparation of the barium salt was developed in order to avoid removal of excess barium by carbon dioxide or sulphuric acid. A mixture of cinchonine *l*-tricatechylarsenate (26·5 g.), methanol (125 c.c.), and barium hydroxide (8 g.) was refluxed for 30 minutes; water (125 c.c.) was then added, and the alcohol slowly distilled off. When 100 c.c. of distillate had been collected, more water (75 c.c.) was added, and a further 50 c.c. of distillate collected. The residue was filtered hot to remove cinchonine, and the filtrate evaporated to dryness at 25 mm. The dry residue (consisting of the required barium salt and barium hydroxide) was extracted with cold absolute alcohol, the undissolved hydroxide removed by filtration, and the barium *l*-tricatechylarsenate precipitated from the filtrate by addition of light petrol as a colourless granular powder: a 0·213% aqueous solution had α −3·74°, $[\alpha]$ −438°.

Phenyl-p-*bromophenylchloroarsine* (XII). Phenyl-*p*-bromophenylarsinic acid was prepared by interaction of diazotised *p*-bromoaniline and phenylarsine oxide in alkaline solution (Blicke and Webster, *J. Amer. Chem. Soc.*, 1937, **59**, 534) and obtained as colourless crystals, m. p. 174—176° (Found: C, 42·7; H, 3·2. Calc. for $C_{12}H_{10}O_2BrAs$: C, 42·25; H, 3·0%). A solution of this acid (82 g.) in methyl alcohol (350 c.c.) and concentrated hydrochloric acid (125 c.c.) was reduced at 100° by a stream of sulphur dioxide, and the crude product cooled, poured into water, and extracted with petrol. Distillation of the dried extract gave the *monochloro-arsine* (XII) as a mobile yellow oil, b. p. 184—186°/0·3 mm., which slowly crystallised when set aside (53·5 g., 65%); crystallisation from alcohol gave colourless needles, m. p. 46—47° (Found: C, 42·3; H, 2·95. $C_{12}H_9ClBrAs$ requires C, 41·9; H, 2·6%).

Phenyl-p-*chlorophenyl*-p-*bromophenylarsine* (XIII). This arsine was prepared in the usual way, a solution of the monochloroarsine (XII) (26 g.) in benzene (100 c.c.) being slowly added to a chilled, agitated Grignard reagent prepared from *p*-chloroiodobenzene (29·5 g., 1·65 mols.) and magnesium (3 g., 1·65 atoms) in ether (80 c.c.). The final mixture was refluxed for 2 hours, cooled, and hydrolysed with ammonium chloride (25 g.) dissolved in water (125 c.c.). The usual working up ultimately gave the *arsine* (XIII) as a pale yellow oil, b. p. 248—252°/0·5 mm., which crystallised after several days (27 g., 85%); recrystallisation from methanol gave colourless crystals, m. p. 64—65° (Found: C, 51·9; H, 2·9. $C_{18}H_{13}ClBrAs$ requires C, 51·5; H, 3·1%).

This arsine by the usual reactions gave the *arsine oxide*, colourless crystals from *cyclo*hexane or *cyclo*hexane–acetone, m. p. 154—156° (Found: C, 49·9; H, 3·2. $C_{18}H_{13}OClBrAs$ requires C, 49·6; H, 3·0%). The *hydroxy-picrate* formed yellow crystals from alcohol, m. p. 184° (Found: C, 43·7; H, 2·4. $C_{24}H_{16}O_8N_3ClBrAs$ requires C, 43·3; H, 2·4%).

Phenyl-p-*tolyl*-p-*chlorophenyl*-p-*bromophenylarsonium iodide* (XIV). A mixture of the above arsine (27·7 g.), *p*-bromotoluene (22·5 g., 2 mols.), and aluminium chloride (8·8 g., 1 mol.) was heated at 185—190° for 1·25 hours. The clear brown salt was then allowed to cool, extracted with cold benzene to remove any unchanged organic reagent, and the residue then extracted with a large volume of boiling water. The latter was filtered, allowed to cool, and poured into a solution of potassium iodide (50 g.) in water (*ca.* 200 c.c.). The pale yellow precipitated iodide was collected and recrystallised from a mixture of water (1200 c.c.) and alcohol (400 c.c.) containing small quantities of potassium iodide and sulphite; the emulsion which formed on cooling finally deposited the colourless crystalline *iodide* (27 g., 64%). A portion was further purified by addition of ether to its alcoholic solution, whereby the iodide separated as a syrup which slowly crystallised; colourless crystals, m. p. 206—208° with preliminary sintering (Found: C, 47·0; H, 2·8. $C_{25}H_{20}ClBrIAs$ requires C, 47·1; H, 3·2%).

A portion of this iodide was converted by the usual method into the *d*-bromocamphorsulphonate; an acetone solution of the latter on evaporation in a desiccator furnished a syrup which slowly formed a hygroscopic brittle glass. This was soluble in many solvents, but separated always as a viscous oil, and could not be crystallised. It was eventually dissolved in alcohol and precipitated by addition of petrol; the syrup thus obtained, when extracted with petrol, again furnished the *sulphonate monohydrate* as a friable glass (Found: C, 49·7; H, 4·4. $C_{35}H_{34}O_4ClBr_2SAs,H_2O$ requires C, 50·1; H, 4·3%).

The *d*-camphornitronate, similarly prepared, also formed a brittle glass which could not be crystallised.

The *l*-*N*-α-phenylethylphthalamate was prepared by interaction of an alcoholic solution of the iodide (1·276 g.) and the silver phthalamate (0·7526 g., 1 mol.) dissolved in 50% aqueous alcohol (60 c.c.). The filtered solution on evaporation gave an oil which formed a brittle glass on extraction with cold petrol, but which, although freely soluble in many solvents, could not be obtained crystalline.

The *l*-menthoxyacetate was similarly prepared, but the final brown viscous syrup could not be crystallised.

The d-*antimonyl tartrate*. Preliminary experiments showed that this salt was the most promising of those investigated, but that although it was soluble in many organic liquids it could be recrystallised only from water. It was therefore prepared by the interaction of silver *d*-antimonyl tartrate (16·9 g.) and the above iodide (26·17 g., 1 mol.) in a hot mixture of water (3 l.) and alcohol (2 l.). The filtrate was evaporated under reduced pressure, the solid residue dissolved in alcohol (100 c.c.), the solution filtered, and the salt reprecipitated by the addition of much ether; the d-*antimonyl tartrate* was thus obtained as an almost colourless solid (28·9 g., 88% of the theoretical) of indefinite m. p. Three recrystallisations from water (800, 500, 200 c.c.) gave in turn 8·6, 2·6, 0·5 g. of the tartrate, still of indefinite m. p. (Found: C, 43·5; H, 2·7. $C_{29}H_{24}O_7ClBrAsSb$ requires C, 43·7; H, 3·0%). The last fraction was dissolved in hot water (200 c.c.), cooled, and treated with potassium iodide (2 g.), but the precipitated arsonium iodide was inactive in alcoholic solution.

4-*Bromo*-o-*xylene*. A solution of *o*-4-xylidine (30 g.) in hot water (250 c.c.) containing sulphuric acid (49 g.) was rapidly chilled to precipitate the amine sulphate as fine crystals, and then maintained at 5—10° and continuously stirred whilst a solution of sodium nitrite (17·5 g., 1 mol.) in water (30 c.c.) was slowly added. Meanwhile, a solution of hydrated copper sulphate (16 g.) and sodium bromide (38·5 g.) in water (250 c.c.) containing sulphuric acid (7·5 g.) was boiled with copper powder (5 g.) under reflux for 3·5 hours, during which a whitish-grey precipitate of cuprous bromide appeared. The refluxing was now stopped, the diazonium solution added with shaking during 30 minutes, the refluxing then continued for 1·5 hours, and the mixture finally distilled in steam. The 4-bromo-*o*-xylene was extracted from the distillate with benzene, washed with alkali, dried, and distilled; colourless liquid, b. p. 206—208° (14·3 g., 31%) (Found: C, 51·1; H, 4·9; Br, 44·9. Calc. for C_8H_9Br: C, 51·9; H, 4·9; Br, 43·2%). This compound has previously been prepared solely by bromination of *o*-xylene (Jacobsen, *Ber.*, 1884, **17**, 2372; Datta and Chatterjee, *J. Amer. Chem. Soc.*, 1916, **38**, 2549).

Phenyl-4-o-*xylyl*-p-*chlorophenyl*-p-*bromophenylarsonium iodide* (XV). A mixture of the arsine (XIII) (8·7 g.), 4-bromo-*o*-xylene (7·7 g., 2 mols.), and aluminium chloride (2·8 g., 1 mol.) was heated at 185—190° for 1·25 hours, and the cold product thrice extracted with boiling water (3 × 250 c.c.). The cold, combined, filtered extracts were slowly added to an aqueous solution of potassium iodide (30 g.), and the arsonium iodide then separated as a colourless precipitate; 7·2 g. (53%). It was purified by dissolution in hot water (700 c.c.) containing alcohol (100 c.c.) and a small amount of potassium iodide and sulphite; cooling gave the *iodide* (XV) as an oil which slowly crystallised but when dry had an indefinite m. p. (Found: C, 47·9; H, 3·45. $C_{26}H_{22}ClBrIAs$ requires C, 47·9; H, 3·4%).

The *d*-bromocamphorsulphonate, prepared in the usual way, formed a friable glass, which had properties very similar to those of the previous sulphonate, and could not be recrystallised.

The l-N-α-*phenylethylphthalamate*, prepared by interaction of the iodide (3·6950 g.) and the silver phthalamate (2·1310 g., 1 mol.) in aqueous alcohol, was isolated as an oil which was then dissolved in alcohol and reprecipitated by addition of ether; the syrup thus obtained solidified when extracted with cold petrol, but the hygroscopic brittle glass (Found: C, 63·4; H, 5·1. $C_{42}H_{36}O_3NClBrAs$ requires C, 63·6; H, 4·6%) could not be crystallised.

The *l*-menthoxyacetate was isolated as a syrup which also could not be crystallised.

The d-*antimonyl tartrate*, prepared and purified similarly to the previous antimonyl tartrate, formed a white crystalline mass from water (Found: C, 44·0; H, 3·4. $C_{30}H_{24}O_7ClBrAsSb$ requires C, 44·4; H, 3·2%). It had an indefinite m. p., and recrystallisation from water did not appear promising.

The arsonium sulphate was prepared by interaction of the iodide and silver sulphate (0·5 mol.) in aqueous alcohol. Evaporation of the filtrate gave a syrup, which was dissolved in alcohol and reprecipitated by ether. This purified syrup, when confined in a desiccator, ultimately gave the sulphate as a friable glass which was very hygroscopic and hence was not analysed.

The *d*-hydrogen tartrate was prepared by treating an aqueous alcoholic solution of tartaric acid with barium hydroxide (0·5 mol.) and then with the arsonium sulphate (0·5 mol.). Evaporation of the filtered solution gave a clear gum, which was extracted with cold acetone and then, when confined in a vacuum, gave the *dihydrate* of the arsonium hydrogen tartrate as a brittle glass (Found: C, 51·2; H, 4·4. $C_{30}H_{27}O_6ClBrAs,2H_2O$ requires C, 50·7; H, 4·4%) which although soluble in various solvents could not be recrystallised.

The l-*tricatechylarsenate*. Acetone solutions of the arsonium sulphate and barium *l*-tricatechylarsenate (1 mol.) were mixed, the barium sulphate allowed to settle, and the supernatant liquid decanted through a filter. Dilution of the filtrate with ether precipitated the *arsonium* l-*tricatechylarsenate* initially as a syrup which readily formed a white solid when extracted with more cold ether (Found: C, 56·9; H, 3·9. $C_{44}H_{24}O_6ClBrAs_2$ requires C, 57·2; H, 3·7%). It was very soluble in acetone, slightly soluble in hot methyl and ethyl alcohols, and insoluble in water. The following experiments were performed on this material.

(i) The salt (1·9 g.) slowly dissolved when boiled with alcohol (150 c.c.); the solution on cooling deposited 0·65 g., which when recrystallised again from alcohol (80 c.c.) furnished 0·15 g. of the salt. A 0·349% solution of the latter in acetone had α −1·25°, $[M]$ −830°. This acetone solution was evaporated to dryness, and the residue taken up in chloroform and shaken with concentrated aqueous potassium iodide solution 6 times to convert the salt into the arsonium iodide. The chloroform solution was then inactive. The low rotation (−830°) of the above salt must presumably have been due to partial racemisation of the anion.

(ii) In view of this result, resolution was now attempted by fractional precipitation of the tri-

catechylarsenate from cold acetone solution by the addition of ether; it was hoped that racemisation of the anion would thus be averted. The following table shows the progress of the fractional precipitation of the arsenate (initial weight, 13·0 g.), the rotation of various fractions being determined in acetone solution.

	Vol. of acetone for dissolution, c.c.	Vol. of ether for precipitation, c.c.	Wt. of ppt., g.	Rotation of ppt. Concn., g./100 g. soln.	α.	[*M*].
A	65	200	9·3	0·224	−2·32°	−2380°
B	45	140	5·7			
C	28	95	4·0	0·236	−2·37	−2320
D	20	60	2·8			
E	14	40	1·95	0·226	−2·21	−2260
F	10	30	—			
G	7	20	0·9	0·223	−2·09	−2160

A portion of fraction G was dissolved in chloroform and shaken six times with saturated aqueous sodium picrate solution and then twice with water. The chloroform solution of the arsonium picrate was dried (Na_2SO_4) but was optically inactive. The solution was then evaporated and the sticky residual yellow *picrate*, when rubbed with water, formed a brittle solid (Found: N, 5·0. $C_{32}H_{24}O_7N_3ClBrAs$ requires N, 5·6%).

A second portion was stirred with warm concentrated hydrochloric acid until it formed a gum; the acid was decanted, and the treatment repeated to ensure conversion into the arsonium chloride. The gummy residue was dissolved in alcohol, filtered from a trace of unchanged arsenate, the alcohol diluted with water, again filtered, and the solution finally added to a concentrated solution of potassium iodide containing some sulphite. The precipitated arsonium iodide was, however, inactive in acetone solution.

The following new compounds were also prepared in the course of this work: *Di*-p-*tolyl*-p-*chlorophenylarsine*, prepared by the action of *p*-chlorophenylmagnesium iodide on di-*p*-tolylchloroarsine, separated from alcohol as colourless crystals, m. p. 125—126·5° (Found: Cl, 10·0. $C_{20}H_{18}ClAs$ requires Cl, 9·6%). m-*Tolyldi*-p-*tolyl*-p-*chlorophenylarsonium iodide* was prepared by interaction of the above arsine (2 g.), *m*-bromotoluene (2 g., 2 mols.), and aluminium chloride (0·74 g., 1 mol.) at 180—190° for 1 hour; the usual extraction ultimately gave the iodide as a monohydrate, colourless crystals from water containing potassium iodide and sulphite; it was also purified by precipitation by ether from a cold methanol solution (Found: C, 53·7; H, 5·05; Cl, 5·8; I, 20·8. $C_{27}H_{25}ClIAs,H_2O$ requires C, 53·6; H, 4·5; Cl, 5·9; I, 21·0%). The salt sintered at *ca.* 120° but did not melt decisively.

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98. *The Chemistry of 2-Chloroalkylamines. Part I. Preparation and General Reactions.*

By W. E. HANBY and H. N. RYDON.

The preparation and properties of a number of *alkyldi-(2-chloroethyl)amines* are described. The dimers formed from these substances on keeping or heating, alone or in methyl alcohol solution, have been shown to be diquaternary piperazinium *salts*. *Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine*, a by-product in one method of preparation of methyldi-(2-chloroethyl)amine, undergoes two types of cyclisation, depending on the reaction conditions, leading to either an isomeric quaternary morpholinium *salt* or a dimeric quaternary piperazinium *salt*. From old aqueous solutions of methyldi-(2-chloroethyl)amine there have been isolated, as picrates, the piperazinium dimer, the original base, and the half-hydrolysis product, *methyl-2-chloroethyl-2-hydroxyethylamine*, which has also been synthesised.

A number of workers (Ward, *J. Amer. Chem. Soc.*, 1935, **57**, 914; McCombie and Purdie, *J.*, 1935, 1217; Mason and Gasch, *J. Amer. Chem. Soc.*, 1938, **60**, 2816) have prepared 2 : 2′ : 2″-trichlorotriethylamine, $N(CH_2{\cdot}CH_2Cl)_3$, and commented on its vesicant properties, while more recently attention has been drawn (Jensen and Lundquist, *Dansk Tidsskr. Farm.*, 1941, **15**, 201; Eisleb, *Ber.*, 1941, **74**, 1433) to the vesicant properties of methyldi-(2-chloroethyl)amine, $NMe(CH_2{\cdot}CH_2Cl)_2$, the hydrochloride of which was first prepared by Prelog and Stepán (*Coll. Czech. Chem. Comm.*, 1935, **7**, 93). The present series of papers describes work carried out with the object of adding to our knowledge of the chemistry of this type of vesicant, which differs from 2 : 2′-dichlorodiethyl sulphide (" mustard gas ") only in the replacement of the thio-ether group by an alkylimino-group.

We have prepared eight representatives of this class of compound; all are basic liquids with vesicant properties which call for suitable precautions in manipulation. Some of their properties, and those of some derivatives, are collected in the Table.

Properties of some 2-chloroalkylamines, NR′R″R‴.

Compound.	R′.	R″.	R‴.	B. p.	pK_a.	M. p. of hydrochloride.	M. p. of picrate.
(I)	Me	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2Cl$	64°/5 mm.	6·1	110°	133°
(II)	Et	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2Cl$	73/4·5 mm.	6·3	141	100
(III)	Pr$^\alpha$	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2Cl$	88—89/5·5 mm.	5·4	—	99
(IV)	Pr$^\beta$	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2Cl$	90/8 mm.	5·7	216	75
(V)	Me	$CH_2{\cdot}CHMeCl$	$CH_2{\cdot}CHMeCl$	82/9 mm.	—	—	110
(VI)	Me	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2Cl$	—	7·1	66	59
(VII)	Me	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2{\cdot}OAc$	78—80/1·5 mm.	—	—	85
(VIII)	Me	$CH_2{\cdot}CH_2Cl$	$CH_2{\cdot}CH_2OH$	—	—	54	76—78

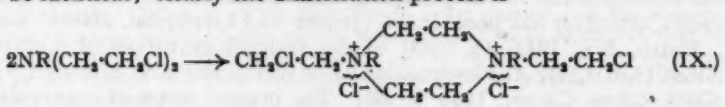
With the exception of (I), none of these *compounds* had previously been described; (IV) was prepared independently of our work, and some months earlier, by Prof. G. H. Coleman of Iowa State University.

Compounds (I) to (IV) were prepared from the corresponding alkyldi-(2-hydroxyethyl)-amines, $NR(CH_2{\cdot}CH_2{\cdot}OH)_2$. This reaction was fully investigated in the case of methyldi-(2-chloroethyl)amine (I), and the best preparative procedure was found to be the use of thionyl chloride in boiling benzene, other chlorinating agents tried (sulphuryl chloride, sulphur monochloride, phosphorus trichloride) giving lower yields; the alkyldi-(2-chloroethyl)amines can be isolated from the reaction product either in the free state, by basification, or as their hydrochlorides, which crystallise from the reaction mixture on cooling. Ethyl- and *iso*propyl-di-(2-hydroxyethyl)amines, required for (II) and (IV), were prepared by the action of ethylene oxide on the appropriate alkylamines in aqueous solution (cf. Knorr and Schmidt, *Ber.*, 1898, **31**, 1074). It was, however, found preferable to prepare methyldi-(2-hydroxyethyl)amine by methylation of di-(2-hydroxyethyl)amine with formaldehyde in the presence of formic acid as hydrogen donator, thus:

$$H{\cdot}CHO + NH(CH_2{\cdot}CH_2{\cdot}OH)_2 + H{\cdot}CO_2H \longrightarrow CH_3{\cdot}N(CH_2{\cdot}CH_2{\cdot}OH)_2 + CO_2 + H_2O$$

This method, which had previously been applied to the methylation of other secondary amines (cf. Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571; Forsee and Pollard, *ibid.*, 1935, **57**, 1788), is preferable to the route from methylamine and ethylene oxide (Knorr and Matthes, *Ber.*, 1898, **31**, 1071) since it avoids the formation of undesirable by-products arising from the reaction of more than two mols. of ethylene oxide with the amine. *n*-Propyldi-(2-hydroxyethyl)amine (Matthes, *Annalen*, 1901, **315**, 127) was prepared by the direct alkylation of di-(2-hydroxyethyl)amine with *n*-propyl bromide, and *methyldi-(2-hydroxy-*n*-propyl)amine*, required for the preparation of (V), by treatment of aqueous methylamine with propylene oxide (it is noteworthy that propylene oxide, unlike ethylene oxide, shows little tendency to react with amines in a molar ratio of more than 2 : 1).

The alkyldi-(2-chloroethyl)amines are all somewhat unstable, depositing solids on keeping at room temperature; the same solid products, which analysis shows to be quaternary ammonium salts with the same empirical formulæ as the parent amines, are formed more rapidly in methyl alcoholic solution. The reaction of the methyl compound (I) in methyl alcohol solution is markedly exothermic and may proceed almost explosively if the quantities of material involved are large. Similar products have been obtained from 2-chloroethylamines by other workers (Knorr, *Ber.*, 1905, **38**, 3135; 1906, **39**, 1420; Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443) who concluded, on the basis of degradative evidence, that they were dimers with the piperazinium dichloride structure [as (IX)]. Comparison of the dimer obtained from methyldi-(2-chloroethyl)amine (I) with synthetic *NN′*-dimethyl-*NN′*-di-(2-chloroethyl)-piperazinium dichloride (IX; R = Me) (Hanby and Rydon, *J.*, 1945, 835) shows the two substances to be identical; clearly the dimerisation process is

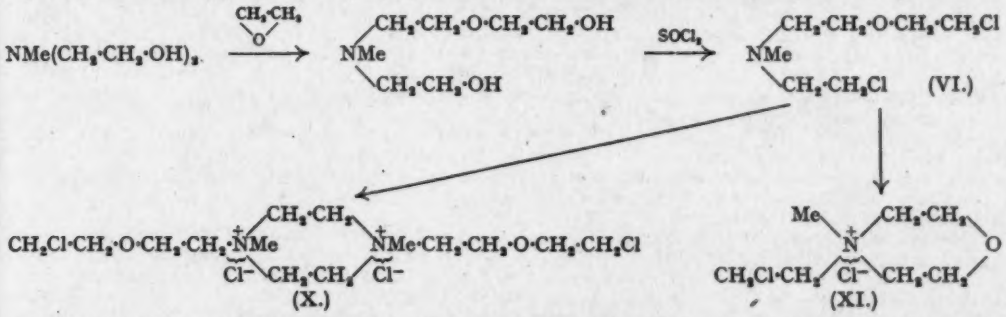


(IX.)

The stereoisomerism of compounds of type (IX) has already been discussed (Hanby and Rydon, *loc. cit.*); in the case of methyldi-(2-chloroethyl)amine, which has been most fully studied, the *cis*-form of the dimer (IX; R = Me) predominates although some of the *trans*-isomer can also be isolated from the reaction product. Comparative studies of the rate of dimerisation of the compounds (I), (II), (III), and (IV) show that the rate falls off very markedly in the order Me > Et > Pr$^\alpha$ > Pr$^\beta$, the relative rates in unevacuated tubes at 100° being in the ratio

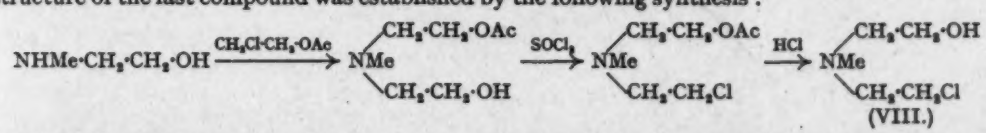
20 : 4 : 2 : 1. Absolute rates cannot be given for the higher homologues with any certainty but the rate of dimerisation of methyldi-(2-chloroethyl)amine in a vacuum at 100°, determined by breaking sealed ampoules under dilute nitric acid and titrating electrometrically with silver nitrate (measurements by Mr. W. R. Waters), is 0·15% per hour; in the presence of air or water the dimerisation is accelerated and the kinetics complicated by side products which have an additional catalytic effect.

The chloroalkylamines formed by chlorinating the dihydroxy-amines produced by the action of more than two mols. of ethylene oxide on methylamine have been studied by Lermit and Moggridge (in the press). As a corollary to their work we have prepared *methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine* (VI) by the method indicated below, and studied its cyclisation.



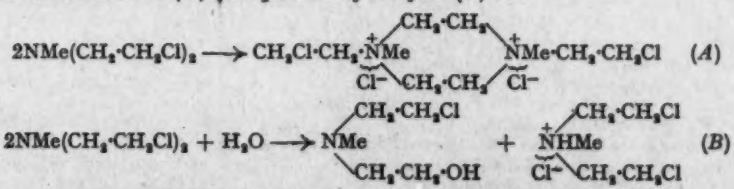
As indicated, there are two modes of cyclisation, yielding either the dimeric *piperazinium* salt (X) or the *morpholinium* salt (XI), which is isomeric with the parent amine (VI); in our hands (XI) was formed when (VI) was heated to 100° or kept without solvent at room temperature, whereas the dimer (X) was the main product when (VI) was kept in methyl alcoholic solution. The structure of (XI) was established by its synthesis from *N*-2-chloroethylmorpholine by way of the methiodide and has since been confirmed by two other independent syntheses (Lermit and Moggridge, *loc. cit.*). A *stereoisomeride* of (X) was obtained by the action of di-2-chloroethyl ether on *NN'*-dimethylpiperazine. The fact that the dimer obtained from (VI) in methyl alcohol is not (XI), which can only exist in one stereoisomeric form, but has similar properties to, although it is not identical with, the synthetic piperazinium salt (X), supports its formulation as one of the two possible stereoisomers of (X).

The detailed mechanism of the action of water on alkyldi-(2-chloroethyl)amines is discussed in Part II (following paper), but it is desirable to outline here some isolation experiments which serve to establish the nature of the end-products of the reaction. Fractional crystallisation of the picrates produced by adding calcium picrate solution * to the neutral solution obtained by keeping methyldi-(2-chloroethyl)amine (I) in 1% aqueous solution for 48 hours gave three main products, *viz.*, the picrate of the dimer (IX; R = Me), the picrate of (I) itself, and the *picrate* of its half-hydrolysis product, *methyl-2-chloroethyl-2-hydroxyethylamine* (VIII). The structure of the last compound was established by the following synthesis:



(VIII) is best prepared by isolation from aged 1% solutions of methyldi-(2-chloroethyl)amine, rather than by synthesis.

Clearly the two main overall reactions involved in the action of water on methyldi-(2-chloroethyl)amine are dimerisation (*A*) and partial hydrolysis (*B*):



* Owing to its greater solubility calcium picrate is superior to sodium picrate for such purposes; a 0·5N-solution can be kept in a warm room and is very convenient for preparative use.

The results of several fractional crystallisation experiments indicate that a 48-hour old 1% solution of methyldi-(2-chloroethyl)amine contains about 25 equiv. % of the dimer (IX; R = Me), 33% of the half-hydrolysis product (VIII), and 20% of the hydrochloride of the original amine (I); it will be shown in the following paper that the remaining 20 equiv. % must be methyldi-(2-hydroxyethyl)amine. In more concentrated solutions there is less hydrolysis (*B*) and more dimerisation (*A*); thus a 79% yield of the picrate of the dimer (X; R = Me) was isolated from an 11% aqueous solution of (I) kept at room temperature for 10 days. The dimer produced by the reaction with water is mainly the *cis*-stereoisomeride, but a much smaller amount of the *trans*-compound is also present.

Experimental.

Preparation of 2-Chloro-alkylamines.—Methyldi-(2-chloroethyl)amine (I). Methyldi-(2-hydroxyethyl)amine was most conveniently prepared as follows. Di-(2-hydroxyethyl)amine (1050 g.; 10 mols.) was mixed with 37·5% w/v formaldehyde (800 c.c.; 10 mols.); to the stirred solution 90% formic acid (425 c.c.; 10 mols.) was added dropwise over 2½ hours, the vigour of the reaction being conveniently regulated by varying the rate of addition. After being heated for 3 hours on the water-bath, the product was distilled, yielding 971 g. (81·5%) of methyldi-(2-hydroxyethyl)amine, b. p. 123—125°/4 mm., n_D^{20} 1·4642 (Found: C, 50·5; H, 10·7; N, 11·25. Calc. for $C_5H_{13}O_2N$: C, 50·4; H, 10·9; N, 11·75%), characterised as its *di*-p-*nitrobenzoate*, rosettes of pale yellow prisms from alcohol, m. p. 112—113° (Found: C, 54·8; H, 4·6; N, 10·4. $C_{19}H_{19}O_8N_3$ requires C, 54·7; H, 4·5; N, 10·1%), and picrate, yellow needles from ethyl acetate, m. p. 95—96°.

Methyldi-(2-hydroxyethyl)amine can also be prepared from ethylene oxide and methylamine (cf. Knorr and Matthes, *Ber.*, 1898, **31**, 1071). A 33% w/v aqueous solution of methylamine (300 c.c.; 3·23 mols.) was cooled in a freezing mixture in a flask fitted with a glass-spiral reflux condenser cooled with circulating ice-water. Ethylene oxide was passed in until the rate of absorption slackened notably (6½ hours), 255 g. (5·8 mols.) having then been taken up. After being kept overnight, the reaction mixture was distilled, yielding 235 g. (62%) of methyldi-(2-hydroxyethyl)amine.

The following is the most satisfactory of many procedures tried for the conversion of methyldi-(2-hydroxyethyl)amine into methyldi-(2-chloroethyl)amine. Methyldi-(2-hydroxyethyl)amine (120 g.; 1 mol.), in benzene (120 c.c.), was added dropwise, under reflux, during 1 hour, to a mixture of thionyl chloride (252 g.; 2·1 mols.) and benzene (120 c.c.); the mixture was then refluxed on the water-bath for 2 hours. Water (120 c.c.) was added to the cooled mixture, which was then basified with 40% sodium hydroxide solution (120 c.c.) and shaken; the aqueous layer was then run off and extracted once more with benzene (50 c.c.). The combined benzene solutions were dried (Na_2SO_4) and distilled, yielding 132 g. (84%) of methyldi-(2-chloroethyl)amine, (I), a mobile colourless liquid with a faint, but characteristic, odour and marked vesicant properties, b. p. 59°/2 mm., 64°/5 mm., 75°/10 mm. (Found: C, 38·6; H, 7·2; N, 9·2; Cl, 45·8. Calc. for $C_5H_{11}NCl_2$: C, 38·5; H, 7·05; N, 9·0; Cl, 45·5%). The hydrochloride, isolated from the cooled reaction mixture by filtration, crystallises from acetone or chloroform in leaflets, m. p. 110°; the picrate forms needles from benzene, m. p. 133°; the *mercurichloride*, prepared by shaking the free base with ice-cold 4% mercuric chloride solution, crystallises from water in needles, m. p. 187—188° (Found: Hg, 35·2. $2C_5H_{11}NCl_2,HgCl_2$ requires Hg, 34·9%).

Ethyldi-(2-chloroethyl)amine (II). Ethylene oxide was passed into ice-cooled 33% w/v ethylamine solution (53 c.c.) until the gain in weight was 35 g. (90 minutes); after 3 hours the product was distilled, yielding 33·8 g. (65%) of ethyldi-(2-hydroxyethyl)amine, b. p. 117—118°/3 mm., $n_D^{16°}$ 1·4670. 86 G. of this intermediate, in chloroform (60 c.c.), were added dropwise over 45 minutes to thionyl chloride (170 g.) in chloroform (80 c.c.); after 1 hours' heating on the water-bath the semi-solid product was cooled and treated with a slight excess of sodium hydroxide solution. The mixture was shaken and separated, and the aqueous layer extracted twice more with chloroform; distillation of the combined dried (Na_2SO_4) extracts yielded the *amine* (II) (87 g.; 79%), as a colourless, mobile, vesicant liquid, b. p. 66°/3 mm., 73°/4·5 mm. (Found: C, 42·9; H, 7·7; N, 8·3; Cl, 42·4. $C_6H_{13}NCl_2$ requires C, 42·4; H, 7·7; N, 8·2; Cl, 41·7%). The *hydrochloride*, isolated in 72·5% yield by adding ether to the reaction product without basifying, crystallised from acetone in rosettes of acicular prisms, m. p. 141° (Found: N, 7·0; Cl, 51·1. $C_6H_{14}NCl_3$ requires N, 6·8; Cl, 51·6%); the *picrate* crystallised from water in feathery clusters of phototropic (yellow to orange) prisms, m. p. 100° (Found: N, 14·3. $C_{12}H_{16}O_7N_4Cl_2$ requires N, 14·0%).

Di-(2-chloroethyl)-n-propylamine (III). *n*-Propyl bromide (32·5 g.) was added, under reflux, with shaking, to a mixture of di-(2-hydroxyethyl)amine (27·5 g.) and anhydrous sodium carbonate (27·5 g.); after 1 hour at room temperature the mixture was refluxed on the water-bath for 4 hours. Alcohol was then added, sodium chloride filtered off, and the filtrate distilled, yielding 20 g. (52%) of di-(2-hydroxyethyl)-*n*-propylamine, b. p. 122—123°/3·5 mm., $n_D^{18°}$ 1·4638. Treatment with thionyl chloride, as described for the ethyl compound, gave a 75% yield of the *dichloro*-compound (III), a colourless vesicant liquid, b. p. 88—89°/5·5 mm. (Found: C, 45·8; H, 8·0; N, 7·9; Cl, 38·4. $C_7H_{15}NCl_2$ requires C, 45·65; H, 8·2; N, 7·6; Cl, 38·6%); the *picrate* crystallised from benzene in thin, phototropic (yellow to orange) needles, m. p. 99° (Found: N, 13·9. $C_{13}H_{18}O_7N_4Cl_2$ requires N, 13·55%).

Di-(2-chloroethyl)isopropylamine (IV). Ethylene oxide (14·4 g.) was passed into an ice-cooled solution of *iso*propylamine (9·6 g.) in water (60 c.c.) during 1 hour. The product was kept at room temperature overnight and then distilled, yielding 17·1 g. (72%) of di-(2-hydroxyethyl)*iso*propylamine, b. p. 129—131°/6 mm., $n_D^{21°}$ 1·4472; the *picrate* crystallised from alcohol in laths, m. p. 139—140° (Found: N, 14·75. $C_{12}H_{18}O_8N_4$ requires N, 14·9%), and the *di*-p-*nitrobenzoate* from alcohol in rosettes of small prismatic needles, m. p. 129—130° (Found: C, 56·8; H, 5·1. $C_{21}H_{23}O_8N_3$ requires C, 56·6; H, 5·2%). Treatment with thionyl chloride, as described for the ethyl compound, gave a 98% yield of *di-(2-chloroethyl)isopropylammonium chloride*, which crystallised from aqueous alcohol in prisms, m. p. 216° (Found:

C, 38·6; H, 6·8. $C_7H_{16}NCl_3$ requires C, 38·1; H, 7·3%). The free base (IV) is a colourless vesicant liquid, b. p. 90°/8 mm.; the *picrate* crystallises from aqueous alcohol in leaflets, m. p. 75° (Found: C, 37·5; H, 4·5. $C_{13}H_{18}O_7N_4Cl_2$ requires C, 37·8; H, 4·4%).

Methyldi-(2-chloro-n-propyl)amine (V). Propylene oxide was added to an aqueous solution (28%) of methylamine (58 g.; 1 mol.) cooled in a freezing mixture. After the initial vigorous reaction had abated the product was kept at room temperature, with occasional ice-cooling in the early stages, for 16 hours and then heated on the water-bath for 3 hours. Distillation yielded 62·7 g. (85%) of *methyldi-(2-hydroxy-n-propyl)amine*, a viscous colourless oil, b. p. 103—104°/6 mm., $n_D^{21°}$ 1·4472 (Found: C, 56·95; H, 11·5. $C_7H_{17}O_2N$ requires C, 57·1; H, 11·5%); the *picrate* crystallised from ethyl acetate–benzene in hygroscopic orange-yellow prismatic needles, m. p. 88° (Found: C, 41·95; H, 5·8. $C_{13}H_{20}O_9N_4$ requires C, 41·5; H, 5·3%). The amine (61 g.) was treated, as usual, with thionyl chloride in benzene, yielding the *dichloroamine* (V) (63·7 g.; 83·5%), b. p. 82°/9 mm. (Found: C, 45·2; H, 8·7; Cl, 39·2. $C_7H_{15}NCl_2$ requires C, 45·6; H, 8·2; Cl, 38·6%); the *picrate* crystallised from benzene in rectangular laths, m. p. 110° (Found: C, 38·2; H, 4·7. $C_{13}H_{18}O_7N_4Cl_2$ requires C, 37·8; H, 4·35%).

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (VI). Ethylene oxide (80 g.) was passed into a mixture of methyldi-(2-hydroxyethyl)amine (240 g.) and water (250 c.c.), the reaction vessel being cooled with running water. Distillation and redistillation yielded methyl-2-hydroxyethyl-2-(2-hydroxyethoxy)ethylamine (75 g.; 23%), b. p. 138°/4 mm., $n_D^{19°}$ 1·4675, characterised as its *di-p-nitrobenzoate*, m. p. 116° (Found: C, 54·2; H, 4·9. $C_{21}H_{23}O_9N_3$ requires C, 54·7; H, 5·0%). This dihydroxy-amine (50 g.), in chloroform (50 c.c.), was added dropwise over 30 minutes to thionyl chloride (81 g.) in chloroform (100 c.c.); the reaction was completed by refluxing on the water-bath for 3 hours. Solvents, etc., were removed by distillation and by keeping the residue in a vacuum desiccator over sodium hydroxide; solution in absolute alcohol (100 c.c.) followed by precipitation with dry ether (500 c.c.) yielded *methyl-2-chloroethyl-2-(2-chloroethoxy)ethylammonium chloride* (56 g.; 77%), m. p. 66° (Found: C, 35·3; H, 6·6; Cl′, 15·0. $C_7H_{15}ONCl_2,HCl$ requires C, 35·5; H, 6·8; Cl′, 15·0%); the *picrate* crystallised from alcohol in flattened needles, m. p. 59° (Found: C, 36·4; H, 4·4. $C_{13}H_{18}O_8N_4Cl_2$ requires C, 36·4; H, 4·2%). The hydrochloride (12 g.) was dissolved in water (30 c.c.), covered with benzene (20 c.c.), and treated, with shaking and cooling, with sodium hydroxide (2 g.) dissolved in a little water; evaporation of the dried benzene solution under reduced pressure at room temperature yielded the free *base* (VI) as an unstable oil which could be kept for a few days at 0° (Found: equiv. by titration, 218·5. $C_7H_{15}ONCl_2$ requires equiv., 200·0).

Methyl-2-chloroethyl-2-hydroxyethylamine (VIII). Methyl-2-hydroxyethylamine was prepared by the following modification of the method of Schotte, Priewe, and Roescheisen (*Z. physiol. Chem.*, 1928, **174**, 119; cf. D.R.-P. 442,413; Pierce and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 790; Pierce, *ibid.*, 1928, **50**, 241). 2-Chloroethyl chloroformate (98 g.) was added in small portions over 15 minutes, with stirring and ice-cooling, to 33% w/v methylamine solution (80 c.c.) containing sodium carbonate (39 g.). After a further 2 hours' stirring the 2-chloroethyl methylcarbamate was extracted with ether, washed with dilute hydrochloric acid and water, dried, and distilled; b. p. 100°/6 mm., 65 g. (69%). This carbamate (120 g.) was added to a solution of potassium hydroxide (195 g.) in 90% alcohol (300 c.c.). After the vigorous reaction had abated the mixture was distilled and redistilled through a long column, yielding 47 g. (72%) of methyl-2-hydroxyethylamine, b. p. 52°/6 mm.

Methyl-2-hydroxyethylamine (47 g.) was heated on the water-bath for 30 minutes with 2-chloroethyl acetate (76 g.) and anhydrous potassium carbonate (43 g.); potassium chloride was filtered from the cooled product and washed with chloroform. Two distillations of the filtrate and washings yielded impure *methyl-2-hydroxyethyl-2-acetoxyethylamine*, b. p. 81—83°/1 mm. (30 g.; 30%) (Found: C, 49·1; H, 8·2; OH, 10·4. $C_7H_{15}O_3N$ requires C, 52·2; H, 9·3; OH, 10·55%). This compound was treated with thionyl chloride in benzene, yielding 6·2 g. (27%) of *methyl-2-chloroethyl-2-acetoxyethylamine* (VII), b. p. 78—80°/1·5 mm. (Found: C, 46·7; H, 7·5; N, 8·05. $C_7H_{14}O_2NCl$ requires C, 46·75; H, 7·8; N, 7·8%), characterised as its *picrate*, yellow prisms from benzene, m. p. 85° (Found: C, 38·7; H, 4·4; Cl, 8·65. $C_{13}H_{17}O_9N_4Cl$ requires C, 38·2; H, 4·2; Cl, 8·7%), and *methiodide*, needles from alcohol, m. p. 150° (decomp.) (Found: C, 30·2; H, 5·5; N, 4·35. $C_8H_{17}O_2NClI$ requires C, 29·9; H, 5·3; N, 4·35%); the structure of (VII) was confirmed by its conversion, on being kept overnight with an equal volume of alcohol, into *cis-NN′*-dimethyl-*NN′*-di-(2-acetoxyethyl)piperazinium dichloride (Hanby and Rydon, *J.*, 1945, 833), m. p. and mixed m. p. 228° (picrate, m. p. and mixed m. p. 188°). The chloro-acetoxy-compound (VII) (5 g.) was hydrolysed by refluxing for 9 hours with concentrated hydrochloric acid (9 c.c.) and water (4·5 c.c.); the resulting solution was evaporated to dryness under reduced pressure and the residue treated with 0·5N-calcium picrate. The crude picrate so precipitated (3·9 g.; 38%) had m. p. 63—65° and crystallised from benzene–ethyl acetate in orange-yellow prisms, m. p. 72—74°, raised to 73—75° on admixture with the picrate isolated from an old aqueous solution of methyldi-(2-chloroethyl)amine (see p. 519).

Dimerisation of 2-Chloroethylamines.—(*a*) Methyldi-(2-chloroethyl)amine (12·5 g.) was kept in methyl alcohol (25 c.c.) for 40 hours at room temperature. The semi-solid product was filtered off, washed with methyl alcohol, and purified by repeated precipitation from water with acetone; the product, m. p. 329° (decomp.) (Found: C, 37·4; H, 7·3; H, 8·9; Cl, 44·15; loss of weight on drying under reduced pressure over phosphoric oxide at 100°, 2·4, 3·1. Found, on material so dried: C, 38·25; H, 7·0; Cl, 45·7. Calc. for $C_{10}H_{22}N_2Cl_4,\frac{1}{2}H_2O$: C, 37·4; H, 7·2; N, 8·7; Cl, 44·3; H_2O, 2·8. Calc. for $C_{10}H_{22}N_2Cl_4$: C, 38·5; H, 7·05; Cl, 45·5%), was identified as *cis-NN′*-dimethyl-*NN′*-di-(2-chloroethyl)piperazinium dichloride (IX; R = Me) by mixed m. p. with a synthetic specimen (Hanby and Rydon, *J.*, 1945, 833) and by mixed m. p. of the derived dipicrate, leaflets or needles from water, m. p. 208° (decomp.). The same dimer is deposited by methyldi-(2-chloroethyl)amine slowly at room temperature and more rapidly on heating.

(*b*) Ethyldi-(2-chloroethyl)amine similarly yielded *NN′-diethyl-NN′-di-(2-chloroethyl)piperazinium dichlorides* (IX; R = Et), m. p. 312° (decomp.) after crystallisation from acetone–methanol (Found: C, 42·2; H, 7·9; N, 8·4. $C_{12}H_{26}N_2Cl_4$ requires C, 42·4; H, 7·7; N, 8·2%), characterised as its *dipicrate*, leaflets from water, m. p. 232° (Found: C, 39·5; H, 4·2. $C_{24}H_{30}O_{14}N_8Cl_2$ requires C, 39·8; H, 4·1%).

(*c*) Di-(2-chloroethyl)-*n*-propylamine similarly yielded NN′-*di*-(2-*chloroethyl*)-NN′-*di*-n-*propylpiperazinium dichloride* (IX; R = Pr^n), needles from methanol, m. p. 315° (decomp.) (Found: C, 45·4; H, 8·3; N, 7·5. $C_{14}H_{30}N_2Cl_4$ requires C, 45·65; H, 8·15; N, 7·6%), and the *dipicrate*, small leaflets from water, m. p. 235° (Found: C, 41·6; H, 4·7. $C_{26}H_{34}O_{14}N_8Cl_2$ requires C, 41·4; H, 4·5%).

Cyclisation Products of Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine.—(*a*) N-*Methyl*-N-2-*chloroethylmorpholinium chloride* (XI). Methyl iodide (8·0 g.) was added gradually, with ice-cooling, to *N*-2-chloroethylmorpholine (6·0 g.; Mason and Block, *J. Amer. Chem. Soc.*, 1940, **62**, 1443), and the mixture was kept overnight at room temperature; the semi-solid product was then rubbed with ether and the solid portion (9·6 g.; 82%) filtered off and dried at 100°. N-*Methyl*-N-2-*chloroethylmorpholinium iodide* crystallised from acetone containing a little water in acicular prisms, m. p. 156—157° (Found: C, 28·8; H, 5·1. $C_7H_{15}ONClI$ requires C, 28·8; H, 5·15%), and was characterised as the *picrate*, long rectangular prisms, aggregating into leaflets, from water, m. p. 171—172° (Found: C, 40·4; H, 4·4; Cl, 8·8. $C_{13}H_{17}O_4N_4Cl$ requires C, 39·75; H, 4·3; Cl, 9·05%). The iodide (2·9 g.), dissolved in water (25 c.c.), was shaken at room temperature for 24 hours with two equivs. of freshly precipitated silver chloride. Evaporation of the filtered solution and crystallisation of the residue from alcohol–ether yielded the *chloride* (XI) as deliquescent prisms, m. p. 169° (decomp.) (Found: C, 42·1; H, 7·5; Cl, 35·6. $C_7H_{15}ONCl_2$ requires C, 42·0; H, 7·5; Cl, 35·5%).

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (VI) solidified completely after heating on the water-bath for 20 minutes. The product was identified as the morpholinium chloride (XI) by crystallisation from alcohol–ether to give a product, in 75% yield, having m. p. 171°, not depressed on admixture with the synthetic product; the identity was further confirmed by conversion into the picrate, m. p. and mixed m. p. 171—172°. The same morpholinium salt was formed, more slowly, when the dichloro-amine (VI) was kept at room temperature.

(*b*) NN′-*Dimethyl*-NN′-*di*-2-(2-*chloroethoxy*)*ethylpiperazinium dichlorides* (X). *NN*′-Dimethylpiperazine (3·5 g.) was heated on the water-bath for 24 hours with 2 : 2′-dichlorodiethyl ether (18 c.c.). The solid product (8·0 g.; 65%; m. p. 330—350°) was collected by filtration, washed with ether, and dried at 100°. Crystallisation from methanol–acetone yielded trans(?)-NN′-*dimethyl*-NN′-*di*-2-(2-*chloroethoxy*)*ethylpiperazinium dichloride* (X) as a micro-crystalline powder, decomp. 365° (Found: C, 41·8; H, 7·25. $C_{14}H_{30}O_2N_2Cl_4$ requires C, 42·0; H, 7·5%); treatment of an aqueous solution with saturated potassium iodide solution and crystallisation of the precipitate from 95% alcohol yielded the corresponding *di-iodide* as a micro-crystalline powder, m. p. 303° (decomp.) (Found: C, 29·3; H, 5·1. $C_{14}H_{30}O_2N_2Cl_2I_2$ requires C, 28·8; H, 5·15%).

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (VI) (2 g.) was kept at room temperature overnight with methanol (5 c.c.); next day much ether was added and the solution filtered. The solid (1·4 g.) was extracted with warm alcohol to remove any morpholinium salt and then crystallised from methanol, yielding cis(?)-NN′-*dimethyl*-NN′-*di*-2-(2-*chloroethoxy*)*ethylpiperazinium dichloride* (X), decomp. 365° (Found: C, 42·2; H, 7·0; N, 6·5. $C_{14}H_{30}O_2N_2Cl_4$ requires C, 42·0; H, 7·5; N, 7·0%); the *di-iodide* crystallised from water in small leaflets, m. p. 289° (decomp.). A mixture of the *cis*- and *trans*-dichlorides melted at 310° but the di-iodides showed no depression of m. p. on admixture.

Action of Water on Methyldi-(2-chloroethyl)amine.—(a) *Isolation of reaction products.* Methyldi(2-chloroethyl)amine (I) (11·5 g.) was shaken with water (1000 c.c.) until solution was complete (a few minutes); the solution was then kept at room temperature for 48 hours. To the solution (2·46 mg. Cl′/c.c.) was added 0·5N-calcium picrate (138 c.c.); fractional crystallisation from water of the immediate precipitate (11·1 g.; m. p. 175—185°) yielded the picrate of the dimer (IX; R = Me) (6·9 g.; 27%; m. p. 193—196°) and a rather impure specimen of the picrate of (I) (3·2 g.; 12%; m. p. 110—113°), which gave the pure picrate, m. p. 127—129°, on further recrystallisation. Three further crops (8·2 g., m. p. 72—74°; 2·9 g., m. p. 68—70°; 1·0 g., m. p. 65—66°) were obtained by concentration of the mother-liquor; these were combined and crystallised from ethyl acetate–benzene, yielding the typical orange prisms of the picrate of methyl-2-chloroethyl-2-hydroxyethylamine (VIII) (9·2 g.; 35%; m. p. 75—77°).

A similar experiment in which 0·1N-sodium picrate was used gave 3·2 g. (24%) of the picrate of the dimer (IX; R = Me) and 1·9 g. (12·5%) of the picrate of (I); it was not possible to isolate the picrate of (VIII) in good yield owing to contamination with sodium picrate.

In another experiment a solution of (I) (113·8 g.) in water (to 1000 c.c.) was kept at room temperature for 10 days and then treated with 0·1N-sodium picrate (720 c.c.); the precipitated picrate (20·1 g.; 79%) gave, on fractional crystallisation from water, only the picrate of the dimer (IX; R = Me), of which 18·4 g. were isolated in five crops (m. p. 202—203°, 203—205°, 201—202°, 199—200°, 198—200°).

(b) *Isolation of stereoisomerides of the dimer* (IX; R = Me). A solution of methyldi-(2-chloroethyl)-amine (226 g.) in water (20 l.) was kept at room temperature for 48 hours, after which time it was evaporated under reduced pressure to 500 c.c. The solid which crystallised on being kept for some time at room temperature was collected, and dried at 100°; this material (8·0 g.; 3·5%; m. p. 328—330°) was identified as the *trans*-dimer (IX; R = Me) by conversion into the picrate, orange needles from water, m. p. and mixed m. p. 225°. To the mother liquor, acetone (5000 c.c.) and water (200 c.c.) were added in several portions; the precipitated solid (59·2 g.; 26·3%; m. p. 328°) was identified as the *cis*-dimer (IX; R = Me) by conversion into the picrate, golden leaflets from water, m. p. and mixed m. p. 203°.

(c) *Preparation of stereoisomerides of the dimer* (IX; R = Me). (i) *Trans.* Methyldi-(2-chloroethyl)amine was kept overnight with an equal volume of methanol; the precipitated dimer was filtered off and washed with acetone. The product was dissolved in the minimum quantity of water at 50—60° and the solution treated with an equal volume of acetone; on cooling, the filtered solution deposited the pure *trans*-dimer (IX; R = Me), identified by conversion into the picrate, m. p. 221° (crude), which crystallised from water in needles, m. p. 225°.

(ii) *Cis.* Methyldi-(2-chloroethyl)amine (30 g.) was kept overnight with methanol (25 c.c.); the precipitated dimer (30 g.) was filtered off, washed with acetone, and dried at 100°. The finely powdered product was shaken vigorously with cold water (75 c.c.); the undissolved portions was shown, by

conversion into the picrate and fractional crystallisation, to contain about 75% of the *trans*- and 25% of the *cis*-dimer. Careful addition of acetone (250 c.c. in all) in three portions to the cold water solution yielded successive crops (0·5 g. + 5·1 g. + 8·0 g. = 13·6 g.) which were all identified as the *cis*-dimer by conversion into the picrate, golden leaflets from water, m. p. and mixed m. p. 206°.

(d) *Preparation of methyl-2-chloroethyl-2-hydroxyethylamine* (VIII). A 48 hour old 1% solution of methyldi-(2-chloroethyl)amine (I) in water (10 l.) was treated with 0·5N-calcium picrate (1304 c.c.). The initial precipitate was filtered off and discarded and the filtrate concentrated under reduced pressure to 2500 c.c. On being kept overnight this solution deposited an initial crop (20·2 g.) of the crude picrate of (I); the mother liquor, on seeding, yielded 80 g. of the practically pure picrate of (VIII), m. p. 72—73°; a further crop (18·5 g.; m. p. 72—73°) was obtained by concentrating the mother liquor to 1000 c.c. *Methyl-2-chloroethyl-2-hydroxyethylammonium picrate* crystallises from ethyl acetate–benzene or water in large orange prisms, m. p. 76—78° (Found: C, 36·4; H, 3·8; N, 15·4. $C_{11}H_{15}O_8N_4Cl$ requires C, 36·0; H, 4·1; N, 15·3%).

The combined crops of picrate (98·5 g.; 41%) were dissolved in hot water and treated with excess hydrochloric acid; the precipitated picric acid was removed by filtration and the remainder by repeated extraction with benzene. Evaporation of the residual solution under reduced pressure yielded methyl-2-chloroethyl-2-hydroxyethylammonium chloride as a thick oil which solidified on long keeping in a vacuum desiccator; the semi-solid product was filtered off and washed with a mixture of equal volumes of *iso*propyl alcohol and dry ether, yielding the very deliquescent *hydrochloride*, m. p. 54° (Found: C, 34·4; H, 7·7; Cl′, 20·8. $C_5H_{12}ONCl,HCl$ requires C, 34·5; H, 7·5; Cl′, 20·4%). The *mercurichloride*, prepared in theoretical yield by treating an aqueous solution of the hydrochloride with aqueous mercuric chloride, crystallised from water in transparent prisms, m. p. 198° (decomp.) (Found: Hg, 45·8. $C_5H_{12}ONCl,HCl,HgCl_2$ requires Hg, 45·0%). Basification of an aqueous solution of the hydrochloride, followed by extraction with chloroform, yielded the free base (VIII), which was, however, extremely unstable. On attempted vacuum distillation the crude product was rapidly converted into a white solid which was identified as a mixture of the stereoisomerides of *NN′*-dimethyl-*NN′*-di-(2-hydroxyethyl)piperazinium dichloride by conversion into the picrate; fractional crystallisation yielded both the *cis*- (m. p. 219—220°) and *trans*- (m. p. 250°) picrates, neither of which showed any depression of m. p. on admixture with synthetic specimens (Hanby and Rydon, *J.*, 1945, 835).

The crude hydrochloride (600 mg.) was refluxed for an hour with thionyl chloride (3 c.c.). Excess of thionyl chloride was removed under reduced pressure, and the residue dissolved in a little water and treated with 0·5N-calcium picrate (8 c.c.). Crystallisation of the precipitate from water yielded the picrate of methyldi-(2-chloroethyl)amine in needles, m. p. 130—131°, mixed m. p. 131—132°.

The crude hydrochloride was similarly treated with acetyl chloride (5 c.c.) and then calcium picrate. Crystallisation of the crude picrate from benzene gave methyl-2-chloroethyl-2-acetoxyethylammonium picrate in lemon-yellow prisms, m. p. 83—84°, unchanged on admixture with the synthetic material (p. 517).

We are indebted to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this paper, to Mr. J. Howarth Williams for investigating the action of a number of chlorinating agents on methyl-(2-hydroxyethyl)amine, and to Mr. J. E. Cave-Browne-Cave for technical assistance; the microanalyses were carried out by Mr. G. Ingram.

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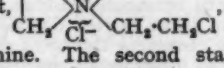
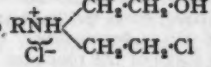
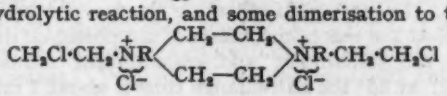
99. *The Chemistry of 2-Chloroalkylamines. Part II. Reactions of Tertiary 2-Chloroalkylamines in Water.*

By W. E. HANBY, G. S. HARTLEY, E. O. POWELL, and H. N. RYDON.

The reactions which take place when dilute aqueous solutions of methyl-, ethyl-, *n*-propyl-, and *iso*propyl-di-(2-chloroethyl)amines, $NR(CH_2{\cdot}CH_2Cl)_2$, are kept at room temperature have been studied. The first stage of the reaction has been shown to be a comparatively fast cyclisation to the quaternary ethyleneimonium salt,  , which is in tautomeric equilibrium with the alkyldi-(2-chloroethyl)amine. The second stage, which is slower, comprises hydrolysis to  and $R\overset{+}{N}H(CH_2{\cdot}CH_2{\cdot}OH)_2\,\overset{\sim}{Cl}^-$, some reversion to the hydrochloride of the starting material, $R\overset{+}{N}H(CH_2{\cdot}CH_2Cl)_2\,\overset{\sim}{Cl}^-$, under the influence of hydrochloric acid produced in the hydrolytic reaction, and some dimerisation to the piperazinium dimer, 

THIS paper is concerned with the study of the reactions which take place at room temperature in dilute aqueous solutions of the tertiary 2-chloroalkylamines, $NR(CH_2{\cdot}CH_2Cl)_2$, the preparation

of which has been described in Part I (preceding paper). Since these substances differ from 2 : 2′-dichlorodiethyl sulphide ("mustard gas") only in the replacement of the thio-ether grouping, $-S-$, by the alkylimino-grouping, $-NR-$, we expected them to react similarly with water. "Mustard gas" is very rapidly hydrolysed in aqueous solution, and Ogston (unpublished work) has shown that its reaction with water is a very clear example of the Hughes–Ingold S_N1 type of aliphatic substitution; we anticipated that the tertiary 2-chloroalkylamines would provide further examples of this type of reaction although it seemed probable that their greater basic strength would enormously reduce the rate of ionisation of the β-chlorine atoms in acid solution, under which conditions the central nitrogen atom would be positively charged.

Our first experiments, carried out with methyldi-(2-chloroethyl)amine, $NMe(CH_2{\cdot}CH_2Cl)_2$, appeared to bear out these expectations. In aqueous solution, measurements of chloride ion concentration showed that the free base disappeared at a rate which was, in the initial stages, independent of the concentration of alkali; reaction with thiosulphate also occurred at the same initial rate. In acid solution no reaction was detectable and, correspondingly, the reaction with water appeared to stop after one of the two chlorine atoms had become ionic. When, however, we attempted to measure the rate of hydrolysis, in the presence of excess alkali, by an electrical conductivity method we obtained results incompatible with this simple view of the reaction mechanism; we found that the conductivity increased with time over the first few minutes and, since the hydroxyl ion is much the most mobile of anions, were forced to conclude that the process was, not a mere replacement of hydroxyl by chloride ions as in simple hydrolysis, but an actual production of additional ions. It will be convenient to discuss our further experiments in two sections, the first devoted to this initial ionisation stage and the second to the subsequent slower reactions.

The Action of Water on Methyldi-(2-chloroethyl)amine.—(1) *The initial reaction.* We will first record a few fundamental physico-chemical properties of the base. By quickly pouring a slight excess of alkali into an aqueous solution of the hydrochloride and observing whether or not a transient turbidity is produced it is possible to estimate the solubility of methyldi-(2-chloroethyl)amine in water as about 1·2% at room temperature; by shaking for a sufficient time very much larger amounts of base can be brought into solution owing to the occurrence of the sequence of reactions described below. Rapid half-neutralisation of an aqueous solution (more dilute than 1%) of the hydrochloride in the presence of indicators gave an approximate pK_a value of 6·1 for the methyldi-(2-chloroethyl)ammonium ion, corresponding to a base dissociation constant of $1{\cdot}2 \times 10^{-8}$. The value of pK_a for methyldi-(2-hydroxyethyl)amine, $NMe(CH_2{\cdot}CH_2{\cdot}OH)_2$, is 8·3, while that for the half-hydrolysis product, $MeN\begin{matrix}CH_2{\cdot}CH_2Cl\\CH_2{\cdot}CH_2{\cdot}OH\end{matrix}$ is presumably intermediate although we were unable to determine it experimentally owing to rapid hydrolysis.

Velocity measurements on the reactions occurring in aqueous solutions of methyldi-(2-chloroethyl)amine were carried out using the following technique.

Reaction of the free base with water was initiated either by rapid addition, with shaking, of a neutralising quantity of barium hydroxide solution to a freshly prepared solution of the hydrochloride, or by rapid additions of water to the free base previously weighed into a dry graduated flask; by the latter method it was possible to effect solution, by shaking, within a few seconds, whereupon the solution was at once made up to volume and transferred to the thermostat. The reaction was arrested, in aliquot samples withdrawn at chosen times, by addition of a known excess of dilute nitric acid. Aliquot parts of the acidified solution were then titrated (*a*) electrometrically with silver nitrate and (*b*) with barium hydroxide, using both bromophenol-blue (mid-pH 3·8) and alizarin-yellow (mid-pH 11·0); the last-mentioned titration had to be carried out rapidly since further reaction occurs at high pH. The silver nitrate required then measures the total chloride ion; the titration to pH 3·8, less the added nitric acid, the acid produced in excess of that required to neutralise the weak bases present; and the titration from pH 3·8 to pH 11·0, the amount of weak base, both reactant and resultant, present; in all cases the acid production measured by titration to pH 3·8 is decreasingly negative during the primary reaction and remains then nearly zero until a very late stage of the reaction.

Typical results of measurements carried out by this procedure on 1% solutions at 10° and 25° are shown in Figs. 1—4; the method of initiating the reaction had no influence on its course. It is clear from the curves that the reaction consists of unimolecular disappearance of weak base, without neutralisation of the remainder, and concomitant unimolecular appearance of a quaternary ammonium salt; at 25° the half-change time is about 7 minutes ($k_1 = 0{\cdot}0016$ sec.$^{-1}$).

That this initial reaction does indeed result in the disappearance of all the methyldi-(2-chloroethyl)amine was demonstrated by the following experiment, which also shows that the reaction is reversed in the presence of hydrochloric acid.

Methyldi-(2-chloroethyl)amine (5·0 g.) was dissolved in water (500 c.c.) by shaking and the resulting solution kept at 25° for 45 minutes, during which time the pH fell from 8·5 to 7·0. The solution was then rapidly extracted five times with benzene; the extract was dried (Na_2SO_4) and the benzene removed under reduced pressure, leaving a very small residue (less than 300 mg.) which was not further examined. N-Hydrochloric acid (32 c.c.) was then added to the benzene-extracted aqueous solution, bringing the pH from 7·0 to 3·0, and the solution was then kept at room temperature for 65 hours. At the end of this time, 5N-sodium hydroxide (6·4 c.c.) was added, bringing the pH to 7·5; the solution, which now smelt strongly of methyldi-(2-chloroethyl)amine, was again extracted five time with benzene immediately after the alkali addition. Evaporation of the dried extract gave a residue (2·5 g.) which was treated with picric acid (3·7 g.) in benzene (50 c.c.). The precipitated picrate (4·9 g.; 40% on the original base) was identified as methyldi-(2-chloroethyl)ammonium picrate by m. p. and mixed m. p. 132—133°.

FIG. 1.

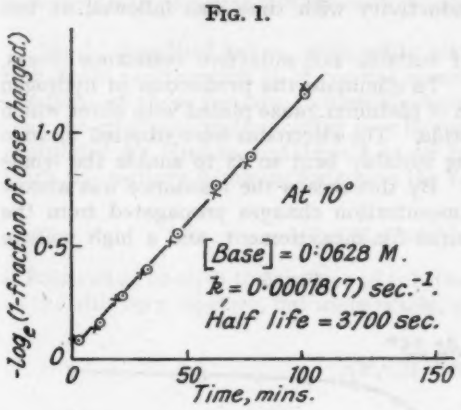
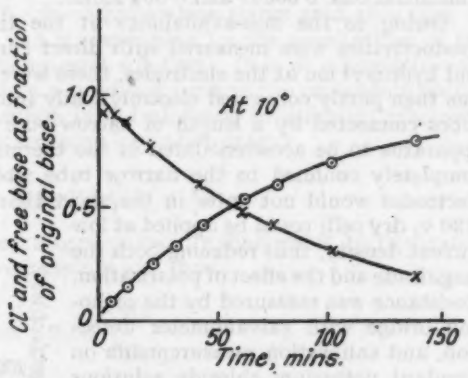


FIG. 2.



×, Free base measurements.
⊙, Cl$^-$ measurements.

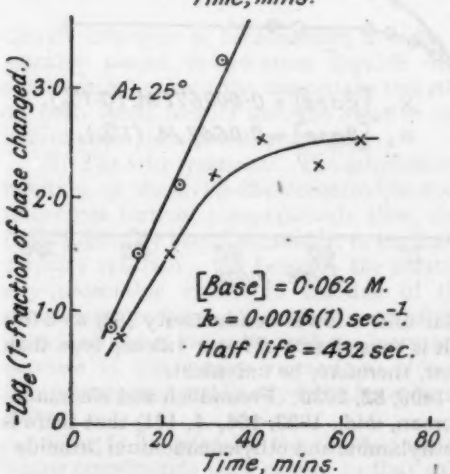


FIG. 3.

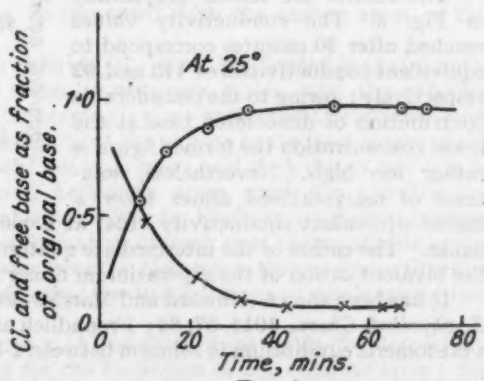


FIG. 4.

It has been shown in Part I (*loc. cit.*) that methyldi-(2-chloroethyl)amine readily undergoes dimerisation to the piperazinium dimer (VI); this compound does not revert to the original amine in the presence of hydrochloric acid, and the experiment just described thus indicates that the intermediate quaternary ammonium salt is not the dimer. Further evidence in support of this conclusion was obtained by investigation of the reaction of methyldi-(2-chloroethyl)amine with sodium thiosulphate. This reaction, followed by titration of excess of sodium thiosulphate with iodine at intervals, was found to proceed initially at the same rate as the formation of the quaternary ammonium salt, but, unlike the latter reaction, continued at a comparable rate until all the chlorine had become ionic. If the free base was allowed to react with water for a short time and a thiosulphate titration was then rapidly carried out, it was found that there was an instantaneous consumption of thiosulphate equivalent to the amount of chloride ion formed by the reaction of the base with water. Presumably the reaction with thiosulphate is of the S_N1 type:

(i) $NMe(CH_2{\cdot}CH_2Cl)_2 \longrightarrow CH_2Cl{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}\overset{+}{C}H_2$ (slow; rate-determining).

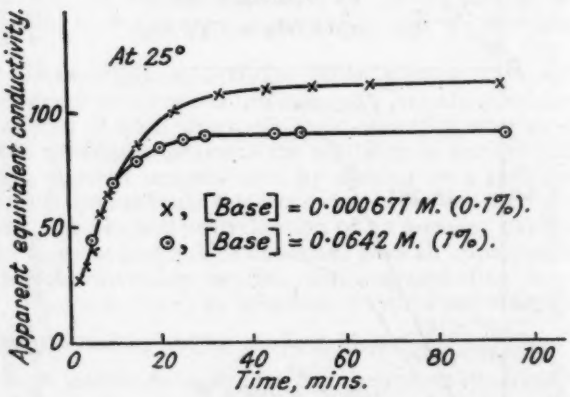
(ii) $CH_2Cl{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}\overset{+}{C}H_2 + S_2O_3^{--} \longrightarrow CH_2Cl{\cdot}CH_2{\cdot}NMe{\cdot}CH_2CH_2{\cdot}S_2O_3^-$ (fast).

The instantaneous reaction of thiosulphate with the intermediate quaternary ammonium salt formed in the reaction of the base with water shows that the latter can replace the carbonium ion in the rapid stage (ii) of the above reaction. This instantaneous reaction provides a useful analytical method for determining the rate of disappearance of the reactive quaternary ammonium salt in the later stages of the reaction and also serves to distinguish it from the much more stable dimer, which does not react with thiosulphate.

Direct evidence for the univalent nature of the intermediate quaternary ammonium cation was obtained as the result of electrical conductivity measurements carried out by Mr. F. J. Kettel. Solutions of methyldi-(2-chloroethyl)amine were made up by direct weighing into dry flasks and addition of water; the change of conductivity with time was followed at two concentrations, 0·00067 and 0·064 molar.

Owing to the non-availability at the time of suitable non-inductive resistance boxes, conductivities were measured with direct current. To eliminate the production of hydrogen and hydroxyl ion at the electrodes, these were made of platinum gauze plated with silver which was then partly converted electrolytically into chloride. The electrodes were situated in wide tubes connected by a length of narrow-bore tubing suitably bent so as to enable the whole apparatus to be accommodated in the thermostat. By this means the resistance was almost completely confined to the narrow tube which concentration changes propagated from the electrodes would not enter in the short time required for measurement, and a high voltage (120 v. dry cell) could be applied at low current density, thus reducing both the magnitude and the effect of polarisation. Resistance was measured by the orthodox bridge with galvanometer detection, and calibration measurements on standard potassium chloride solutions gave results in good agreement with accepted values.

FIG. 5.



The results are shown graphically in Fig. 5. The conductivity values reached after 60 minutes correspond to equivalent conductivities of 113 and 92 respectively; owing to the considerable contribution of dissociated base at the lower concentration the former figure is rather too high. Nevertheless, solutions of recrystallised dimer show a higher equivalent conductivity (124) at 0·00067 molar and a lower conductivity (82) at 0·064 molar. The cation of the intermediate quaternary salt is thus clearly of lower valence type than the bivalent cation of the piperazinium dimer; it must, therefore, be univalent.

It has been shown (Howard and Marckwald, *Ber.*, 1899, **32**, 2036; Freundlich and Neumann, *Z. physikal. Chem.*, 1914, **87**, 69; Freundlich and Saloman, *ibid.*, 1933, **166**, *A*, 161) that there is a tautomeric equilibrium in solution between 2-bromoethylamine and ethyleneimonium bromide:

$$NH_2{\cdot}CH_2{\cdot}CH_2Br \rightleftharpoons \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!\overset{+}{N}H_2\,Br^-$$

There seems to be no reason why a similar equilibrium should not be set up in aqueous solutions of alkyldi-(2-chloroethyl)amines, thus:

$$CH_2Cl{\cdot}CH_2{\cdot}NR{\cdot}CH_2{\cdot}CH_2Cl \rightleftharpoons \begin{matrix} CH_2 \\ | \\ CH_2 \end{matrix}\!\!>\!\overset{+}{N}R{\cdot}CH_2{\cdot}CH_2Cl\ \overset{-}{Cl}$$

(I.) (II.)

We accordingly identify * the reactive intermediate quaternary ammonium salt formed rapidly in aqueous solutions of methyldi-(2-chloroethyl)amine, (I; R = Me), with the quaternary salt, *methyl-2-chloroethylethyleneimonium chloride*, (II; R = Me). It will be seen that the

* Since this work was carried out, in the summer of 1942, Goldberg (*J.*, 1945, 826) has postulated a similar quaternary ethyleneimonium salt as an intermediate in some reactions of diethyl-2-chloroethylamine.

ethyleneimonium salt (II) fulfils all the requirements of the experimental findings; it is clear, also, that it must be the main organic component of a 1% solution of the amine (I; R = Me) which has been kept at 25° for 45 minutes, and we have been able to isolate a *mercurichloride*, probably that of (II; R = Me), from such a solution, as follows.

A solution of methyldi-(2-chloroethyl)amine (2·5 g.) in water (250 c.c.) was kept at 25° for 45 minutes; mercuric chloride (9 g.), dissolved in hot water (45 c.c.), was then added and the solution rapidly cooled. Crystallisation of the precipitate from hot water yielded N-*methyl*-N-2-*chloroethylethyleneimonium chloride bismercurichloride* in flattened needles, m. p. 197° (decomp.) (Found: Hg, 57·5. $C_5H_{11}NCl_2,2HgCl_2$ requires Hg, 57·4%); the m. p. was depressed to 163—170° on admixture with the mercurichloride of methyldi-(2-chloroethyl)amine, m. p. 187—188° (Part I, *loc. cit.*).

Work, described below, with other alkyldi-(2-chloroethyl)amines shows that this type of ring–chain tautomerism is of general occurrence and is responsible for the peculiarities of the reactions of these tertiary 2-chloroalkylamines in aqueous solution. It is of interest to note that the ethyleneimonium cation may be regarded as a stabilised form of the carbonium cation postulated by Hughes and Ingold as an intermediate in S_N1 aliphatic substitution reactions. With the tertiary 2-chloroalkylamine the rate-determining ionisation stage:

$$NR_2\cdot CH_2\cdot CH_2Cl \rightleftharpoons NR_2\cdot CH_2\cdot \overset{+}{C}H_2 + Cl^-$$

is followed at once, in the absence of substances reacting more rapidly than water, by cyclisation to the still very reactive, but more stable, ethyleneimonium ion, thus:

$$NR_2\cdot CH_2\cdot \overset{+}{C}H_2 \rightleftharpoons R_2\overset{+}{N}\begin{matrix}CH_2\\|\\CH_2\end{matrix}$$

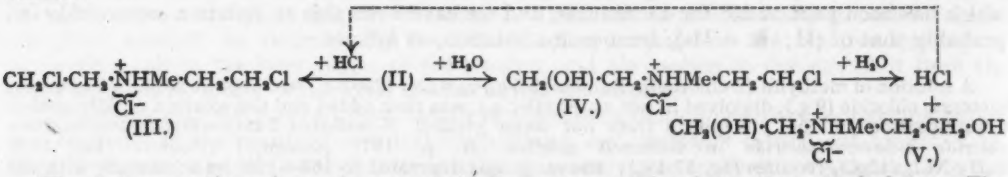
Clearly this type of tautomerism is to be expected whenever there is, in the carbonium ion, a suitably placed hetero-atom capable of carrying a positive charge; the position of the equilibrium between the carbonium and ethyleneimonium (or other heteronium) ions will depend on both steric factors and the relative tolerance, as compared with the carbon atom, of the hetero-atom for a positive charge.

(2) *The later reactions.* The ethyleneimonium chloride (II; R = Me) formed in the primary reaction of methyldi-(2-chloroethyl)amine with water is not very stable, and the solution undergoes further, comparatively slow, changes on keeping; these subsequent reactions have, in fact, already begun somewhat to confuse the simplicity of the picture in the later stages of the primary reaction. On keeping, the solution slowly becomes more acid, but this is not due to any detectable extent to reaction of the second β-chlorine atom since the chloride ion concentration does not increase even after several days. The dual-indicator titration method described above indicates that the main reaction is formation of weak base hydrochloride at the expense of quaternary ammonium chloride; concurrently the rapid thiosulphate titration figure diminishes and finally falls almost to zero, indicating the disappearance of ethyleneimonium salts.

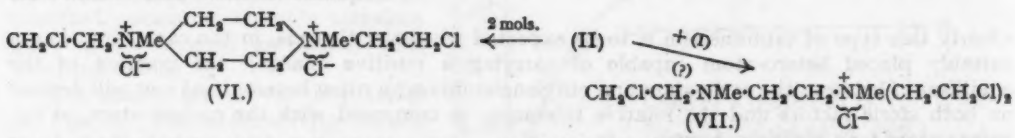
After 48 hours at 25° the chloride ion content of a 1% solution of methyldi-(2-chloroethyl)-amine corresponds very closely to that calculated for the ionisation of one chlorine atom; the pH of the solution has changed from about 7·0 (45 minutes after initiation of the reaction) to about 5·5, and titration shows that 55—65% of the salts present are weak-base hydrochlorides. The amount of such hydrochlorides present when a steady state is reached decreases with rise of temperature, being about 40 equivs. % at 0° and 80 equivs. % at 60°, both in 1% solution. The proportion of weak-base hydrochlorides also decreases with increasing initial concentration of methyldi-(2-chloroethyl)amine; an 11% solution, made up by shaking until all the free base had dissolved, contained less than 10 equivs. % of weak base hydrochloride after 72 hours at 25°. The isolation experiments described in Part I (*loc. cit.*) show that, after 48 hours at 25°, a 1% solution of methyldi-(2-chloroethyl)amine contained about 35 equivs. % of the hydrochloride of the half-hydrolysis product (IV), and 25 equivs. % of the hydrochloride of the original amine (III).

These results all indicate that, on keeping, the ethyleneimonium salt (II) undergoes hydrolysis to the half-hydrolysis product (IV); the hydrochloric acid liberated in this process brings about some reversal of the ring–chain tautomerism, and methyldi-(2-chloroethyl)ammonium chloride (III) also appears in the solution. The constancy of the chloride-ion concentration requires stoicheiometrically that methyldi-(2-hydroxyethyl)amine hydrochloride (V) must also be

present, in amount equivalent to (III). We may thus depict the hydrolytic reactions as follows :



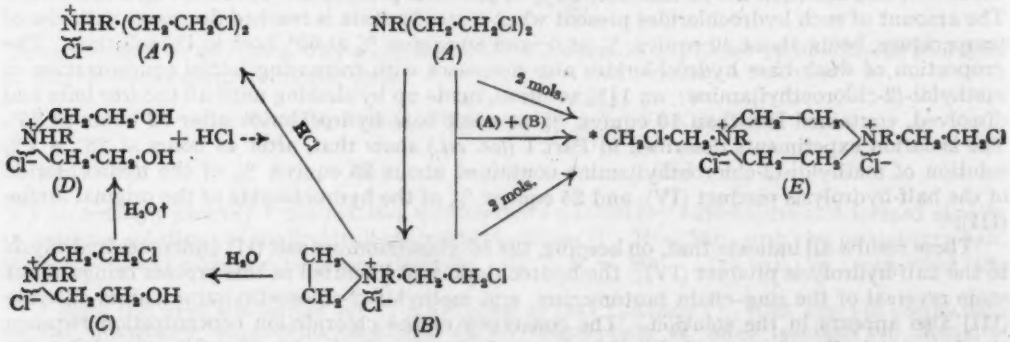
The later reactions in water are not, however, restricted to these hydrolyses. The instantaneous thiosulphate titre reaches effectively zero, and acidimetric titrations reach their final value, in about 70 hours at 25° when weak base hydrochlorides do not account for the whole of the chloride ion present in the solution. Part of the ethyleneimonium chloride (II) must, therefore, have been converted into a stable quaternary ammonium salt. In Part I (*loc. cit.*) we describe the isolation, as picrate, from 1% solutions kept at 25° for 48 hours, of some 25 equivs. % of the piperazinium dimer (VI), in both *cis*- and *trans*-forms; clearly this dimer is the main stable quaternary ammonium salt present in the final equilibrium solution. The amount of this dimer increases with increasing initial concentration of the solution, and an 11% solution was shown to contain 79 equivs. % after 10 days at room temperature. An unexpected finding with this 11% solution was that the chloride-ion concentration became stabilised at about 6% less than half the total chlorine present; this may be due to some formation of the open-chain dimer (VII). The formation of the piperazinium dimer (VI) probably takes place by interaction of two molecules of the ethyleneimonium salt (II), although other mechanisms are not excluded, and we may thus write the dimerisation reactions occurring in the later stages of the reaction with water as follows :



It is emphasised that, in a 1% solution, the analytical results indicated the presence of not more than about 1 equiv. % of (VII); furthermore, we were quite unable to isolate (VII), or any derivative of (VII), from aged solutions of methyldi-(2-chloroethyl)amine. In the generalised scheme given below, which combines all the processes known to take place in dilute (*ca.* 1%) solutions of alkyldi-(2-chloroethyl)amines, we have accordingly omitted the open-chain dimer (VII); in the generalised scheme we indicate also the possibilities that the piperazinium dimer (VI) may arise, wholly or in part, from (I) without the intervention of (II).

The mechanism of dimer formation might be decided by measurements in aqueous alcohol when dimerisation, at least in the case of the methyl compound, is the almost exclusive reaction. [One of us (E. O. P.) in collaboration with Dr. C. L. Hewett, examined the dimerisation in the radically different solvent benzene; the reaction was then found to follow more closely the second-order equation than the first.]

The Action of Water on Some Other Alkyldi-(2-chloroethyl)amines.—The following reaction scheme based on the work just described shows diagrammatically the various processes which occur when a dilute (*ca.* 1%) solution of an alkyldi-(2-chloroethyl)amine is kept at room temperature :



* Alternative routes. † A further ethyleneimonium salt may intervene in this reaction.

The following analytical procedure, which is unfortunately not applicable to methyldi-(2-chloroethyl)amine (*A*; R = Me) owing to unfavourable values of the dissociation constants of the hydrolysis products (*C* and *D*; R = Me), has enabled us to follow approximately the course of events in solutions of ethyl-, *n*-propyl- and *iso*propyl-di-(2-chloroethyl)amines, (*A*; R = Et, Pr$^{\alpha}$, Pr$^{\beta}$):

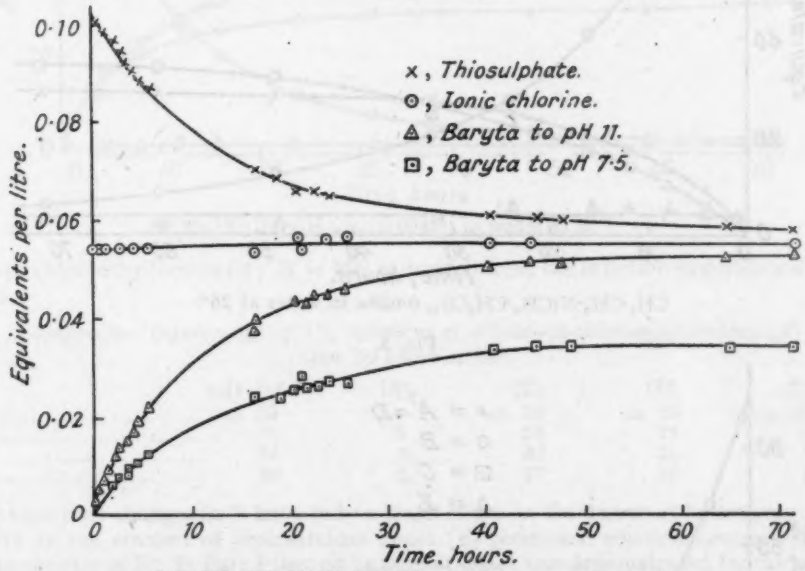
The base under investigation (5·0 g) was weighed out and made up to 500 c.c. with water at 25°; the mixture was shaken or stirred vigourously until solution was complete. The time of complete solution was taken as zero time for the experiment. The resulting solution was kept at 25° and aliquots removed from time to time for the following titrations:

(i) *Sodium thiosulphate.* 10 C.c. of the reaction solution were added to 15 c.c. of 0·1N-sodium thiosulphate containing suspended chalk. After 30 minutes at room temperature, the excess of thiosulphate was titrated with 0·1N-iodine.

(ii) *Silver nitrate.* 10 C.c. samples were removed, treated with 10 c.c. of 0·1N-nitric acid, and titrated electrometrically with 0·1N-silver nitrate.

(iii) *Barium hydroxide.* Two 10 c.c. samples were removed and run into 10 c.c. lots of 0·1N-nitric acid. One sample was then titrated to pH 7·5 using bromothymol-blue, and the other to pH 11·0 using alizarin yellow.

FIG. 6.



$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_2{\cdot}CH_2Cl)_2$, 0·0546M *in water at* 25°.

The experimental results were plotted graphically, making allowance in the barium hydroxide titrations for the added nitric acid, and the composition of the solution at various times was calculated, using the smoothed curves, as follows. Let a = original concentration of (*A*), b = sodium thiosulphate titre, c = barium hydroxide titre to pH 7·5 and d = barium hydroxide titre to pH 11·0, all in equivs./l. Then

$a = [A] + [A'] + [B] + [C] + [D] + [E]$

$b = 2([A] + [A']) + 2\,[B] + [C]$ (since, under the experimental conditions used, *A*, *A'*, and *B* react with two equivalents, and *C* with one equivalent, of thiosulphate).

$c = [A] + [A'] + [B]$ (the alternative possibility that $c = [A] + [A']$ is ruled out by the fact that c was alway larger than $d - c$; the whole of *B*, and not only a part, must have titrated before pH 7·5 since the bromothymol-blue end-point was always sharp).

$d - c = [D] = [A] + [A']$ (this equality follows from the constancy of Cl^-).

Solving for $[A]$ . . . . $[E]$ we find

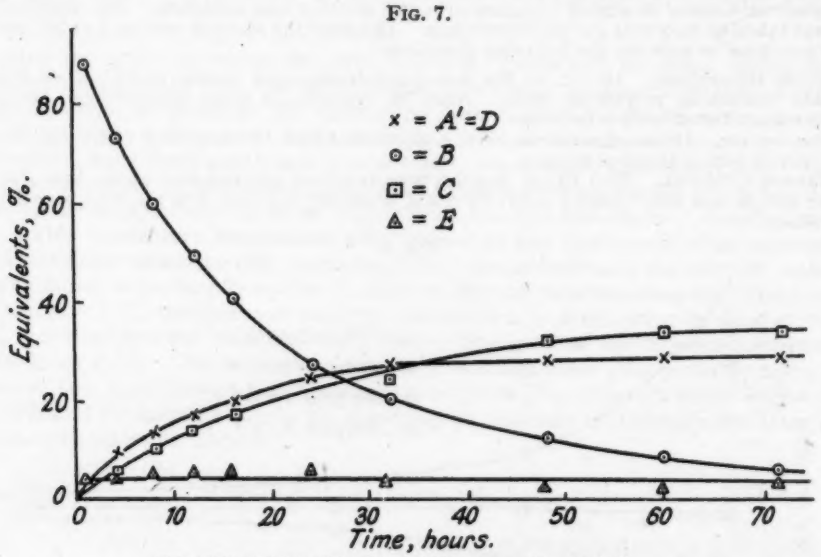
$$[A] + [A'] = [D] = d - c \qquad [C] = 2c - d$$

$$[B] = \frac{b - d}{2} \qquad [E] = \frac{2a - b - d}{2}$$

We wish to emphasise that the values obtained in this way are subject to rather large experimental errors, depending as they do on differences between titres each of which may themselves be in error; the values obtained do, however, at least give a good general picture of the trend of events in the solutions studied.

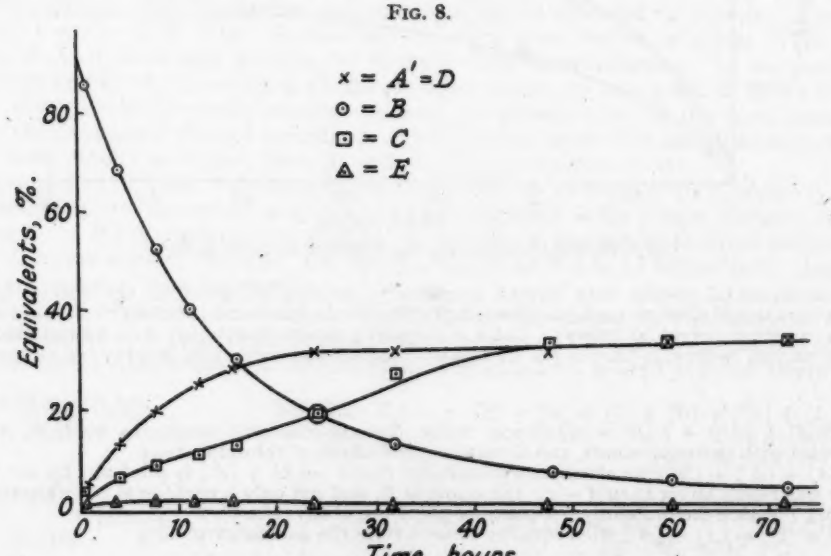
The experimental values obtained for (*A*, R = Pr$^{\alpha}$) are shown in Fig. 6, and the calculated equivalent percentages of the various components for 1% solutions of the three bases (*A*; R = Et, Pr$^{\alpha}$ and Pr$^{\beta}$) in Figs. 7, 8, and 9. In every case rapid cyclisation to the ethyleneimonium chloride (*B*) occurs during solution of the base; some dimer (*E*) is formed concurrently but the absolute amount is too small to enable any conclusion to be drawn as to whether or not further dimer is formed from *B*. Unfortunately time did not permit the extension of the rapid

FIG. 7.



$CH_3 \cdot CH_2 \cdot N(CH_2 \cdot CH_2Cl)_2$, 0·059M in water at 25°.

FIG. 8.



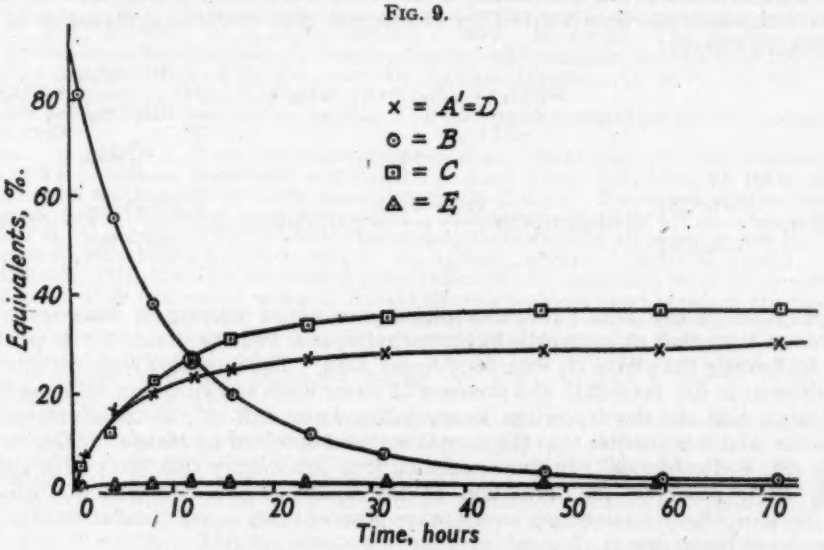
$CH_3 \cdot CH_2 \cdot CH_2 \cdot N(CH_2 \cdot CH_2Cl)_2$, 0·0546M in water at 25°.

thiosulphate titration to the later stages of the reaction with the methyl compound when dimer is formed in much larger amount. This rapid cyclisation reaction is followed by the hydrolytic disappearance of *B*; the process is formally unimolecular, with the following first-order velocity constants:

A; R =	Et.	Pr$^{\alpha}$.	Pr$^{\beta}$.
$k_1 \times 10^5$ (secs.$^{-1}$)	1·37	1·81	2·61

The formation of the reaction products proceeds, as shown in Figs. 7, 8, and 9, until a steady state is reached in about 70 hours at 25°; the compositions of the resulting equilibrium solutions are summarised in the following table, to which have been added the probable values for

FIG. 9.



$CHMe_2 \cdot N(CH_2 \cdot CH_2Cl)_2$, 0·0545M in water at 25°.

methyldi-(2-chloroethyl)amine (*A*; R = Me) estimated from the isolation experiments described in Part I:

Composition (equivs. %) of 1% solutions of alkyldi-(2-chloroethyl)amines (A) after 70 hours at 25°.

R.	(*A*) + (*A'*).	(*B*).	(*C*).	(*D*).	(*E*).
Me	*ca.* 20	—	*ca.* 35	*ca.* 20	*ca.* 25
Et	28	5	35	28	4
Pr$^{\alpha}$	32	3	32	32	1
Pr$^{\beta}$	30	2	37	30	1

It will be seen that changes in R have only a small effect on the degree of hydrolysis but have a large effect on the amount of piperazinium dimer (*E*) produced, which decreases rapidly with increase in the size of R; in Part I (*loc. cit.*) a similar effect was demonstrated for the rate of heat dimerisation of the bases. Clearly the effect depends on the size of R rather than on its electron-releasing power and is therefore probably steric in nature.

We are indebted to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this work, and to Messrs. J. E. Cave-Browne-Cave and J. W. G. McLauchlan for technical assistance.

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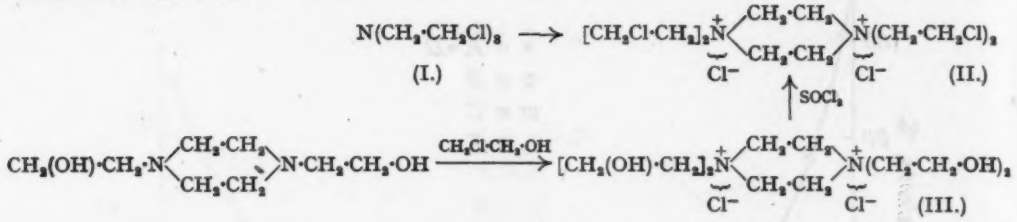
100. *The Chemistry of 2-Chloroalkylamines. Part III. The Dimerisation and Hydrolysis of 2 : 2' : 2''-Trichlorotriethylamine.*

By C. W. CRANE and H. N. RYDON.

The solid deposited by dry 2 : 2' : 2''-trichlorotriethylamine on being kept or heated has been identified as the dimer, NNN'N'-*tetra*-(2-*chloroethyl*)*piperazinium dichloride* (II), by comparison with a synthetic specimen. In contrast to the alkyldi-(2-chloroethyl)amines (Part I, this vol., p. 513) the main action of methyl alcohol on 2 : 2' : 2''-trichlorotriethylamine is not dimerisation but substitution. The action of water on 2 : 2' : 2''-trichlorotriethylamine is shown to yield a little dimer, much 2-chloroethyldi-(2-hydroxyethyl)amine and some 2 : 2' : 2''-trihydroxytriethylamine.

Mason and Gasch (*J. Amer. Chem. Soc.*, 1938, **60**, 2816) noted that, on long keeping, 2 : 2′ : 2″-trichlorotriethylamine (I) deposited a solid which they did not attempt to identify. Work on the dimerisation of alkyldi-(2-chloroethyl)amines (Part I, *loc. cit.*) made it very probable that this solid was the dimer, NNN′N′-*tetra*-(2-*chloroethyl*)*piperazinium dichloride* (II); this conclusion has been verified by comparison with material synthesised as outlined in the following scheme:

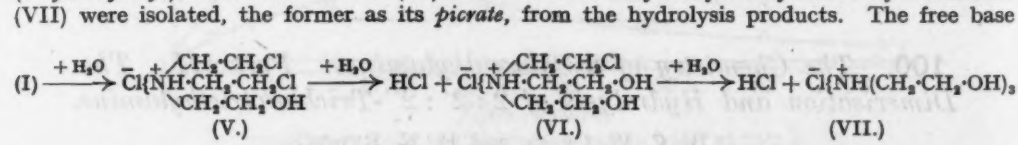


The dimerisation of dry 2 : 2′ : 2″-trichlorotriethylamine on keeping or heating is a much slower process than that of methyldi-(2-chloroethyl)amine, and the dimer (II) is most readily obtained by heating the amine (I) with 98% formic acid. The foregoing observations apply to the dimerisation of dry material; the presence of water leads to hydrolysis with the liberation of hydrochloric acid and the deposition, in crystalline form, of 2 : 2′ : 2″-trichlorotriethylamine hydrochloride, and it is possible that the crystalline solid obtained by Mason and Gasch (*loc. cit.*) was really this hydrochloride. In this connexion it is noteworthy that McCombie and Purdie (*J.*, 1935, 1217) observed the formation of the hydrochloride during the distillation of 2 : 2′ : 2″-trichlorotriethylamine; we have always observed this in the distillation of all but the driest samples of the amine.

Unlike methyldi-(2-chloroethyl)amine, 2 : 2′ : 2″-trichlorotriethylamine undergoes only a little dimerisation in methyl alcohol solution, the main reaction being substitution leading to the formation of *di*-(2-*chloroethyl*)-2-*methoxyethylamine* (IV). This tendency towards substitution rather than dimerisation is probably to be ascribed to the comparative weakness of 2 : 2′ : 2″-trichlorotriethylamine as a base [$pK_a = 3{\cdot}0$ as compared with $pK_a = 6{\cdot}1$ for methyldi-(2-chloroethyl)amine] and the consequent relative reluctance of the nitrogen atom to take part in ammonium salt formation. This view is strengthened by the observation that the methanolysis product (IV), which is a stronger base ($pK_a = ca.\ 5{\cdot}5$), differs from 2 : 2′ : 2″-trichlorotriethylamine in readily dimerising in methyl alcohol to yield NN′-*di*-(2-*chloroethyl*)-NN′-*di*-(2-*methoxyethyl*)*piperazinium dichloride*.

Owing to the relative insolubility of 2 : 2′ : 2″-trichlorotriethylamine in water we were unable to carry out so complete a study of the reaction with water as was possible with the alkyldi-(2-chloroethyl)amines (Part II, preceding paper). However, such results as could be obtained indicated that, in an eventually 1% solution, only about 4% of the dimer (II) was formed; otherwise the reaction appeared to be, formally at least, a simple hydrolysis. We were unable to determine whether or not an ethyleneimonium salt intervened in the early stages. The first equivalent of hydrochloric acid was liberated in about 20 hours, during much of which time two phases were present, and was followed by a slower further liberation of acid, which was still proceeding after 240 hours at 25° when nearly 1·5 equivalents of hydrochloric acid had been liberated.

Of the three expected hydrolysis products, (V), (VI), and (VII), two, *viz.*, 2-*chloroethyldi*-(2-*hydroxyethyl*)*ammonium chloride* (VI) and 2 : 2′ : 2″-trihydroxytriethylamine hydrochloride (VII) were isolated, the former as its *picrate*, from the hydrolysis products. The free base



derived from (VI) resembles the methanolysis product (IV) in rapidly dimerising in alcoholic solution to yield NNN′N′-*tetra*-(2-*hydroxyethyl*)*piperazinium dichloride* (III) which was identified by comparison with the synthetic product; this identity serves also to confirm the structure assigned to (VI). A number of unsuccessful attempts were made to synthesise (V) and (VI); in the course of this work 2-*acetoxyethylamine* and *phthalo*-2-*acetoxyethylimide* were prepared, and the preparation of 2 : 2′-diacetoxydiethylamine hydrochloride was improved.

Experimental.

Dimerisation of 2 : 2′ : 2″-Trichlorotriethylamine.—The amine (10 g.) was heated on the water-bath for 5½ hours with 98% formic acid (2·3 g.). The brown sticky product was rubbed with acetone and filtered; two precipitations from water with acetone yielded NNN′N′-*tetra*-(2-*chloroethyl*)*piperazinium dichloride* (II), m. p. 331° (decomp.) not depressed on admixture with the synthetic product (below) (Found: C, 35·3; H, 5·75. $C_{12}H_{24}N_2Cl_6$ requires C, 35·2; H, 5·9%). The identity was further confirmed by conversion into the *dipicrate*, orange-yellow prisms from dilute acetone, m. p. 222° (decomp.) not depressed on admixture with the synthetic product (Found: C, 36·8; H, 3·3; N, 14·0. $C_{24}H_{28}O_{14}N_8Cl_4$ requires C, 36·3; H, 3·5; N, 14·1%).

The same product was obtained by heating 2 : 2′ : 2″-trichlorotriethylamine in a sealed tube at 100° for 20 days.

Synthesis of NNN′N′-*Tetra*-(2-*chloroethyl*)*piperazinium Dichloride.*—*NN′*-Di-(2-hydroxyethyl)-piperazine (2·6 g.; Adelson, MacDowell, and Pollard, *J. Amer. Chem. Soc.*, 1935, **57**, 1988) was heated on the water-bath for 33 hours with ethylene chlorohydrin (7·2 g.). The cooled mixture was treated with acetone and the precipitated, very deliquescent, piperazinium salt (III) (300 mg.), m. p. 220—221°, characterised as its picrate, NNN′N′-*tetra*-(2-*hydroxyethyl*)*piperazinium dipicrate*, yellow needles from water, m. p. 215—216° (Found: C, 39·9; H, 4·7. $C_{24}H_{32}N_8O_{18}$ requires C, 40·0; H, 4·45%).

The dichloride (III) (250 mg.) was heated under reflux on the water-bath for 7 hours with thionyl chloride (5 c.c.); after removal of excess of thionyl chloride under reduced pressure, the product was dissolved in water and precipitated with acetone. NNN′N′-*Tetra*-(2-*chloroethyl*)*piperazinium dichloride* (II), m. p. 330° (decomp.), crystallised from dilute acetone in micro-crystals (Found: C, 34·8; H, 6·4; N, 6·3. $C_{12}H_{24}N_2Cl_6$ requires C, 35·2; H, 5·9; N, 6·85%); the *dipicrate* crystallised from water in orange-yellow prisms, m. p. 224° (decomp.) (Found: C, 37·0; H, 3·5; N, 13·75. $C_{24}H_{28}O_{14}N_8Cl_4$ requires C, 36·3; H, 3·5; N, 14·1%).

Action of Methanol on 2 : 2′ : 2″-Trichlorotriethylamine.—2 : 2′ : 2″-Trichlorotriethylamine (27 g.) was refluxed on the water-bath for 30 hours with methanol (75 c.c.). After evaporation under reduced pressure, treatment of the product with acetone gave 1·5 g. (5%) of the dimer (II), m. p. 330—331° after recrystallisation from aqueous acetone; evaporation of the acetone mother-liquor and crystallisation of the residue from benzene yielded 25·5 g. (82%) of *di*-(2-*chloroethyl*)-2-*methoxyethylammonium chloride*, leaflets m. p. 133—134° (Found: C, 36·2; H, 6·6; N, 5·8; Cl, 45·0. $C_7H_{16}ONCl_3$ requires C, 35·5; H, 6·8; N, 5·9; Cl, 45·0%). This was dissolved in water and basified; the liberated base was extracted with benzene, dried, and distilled, yielding 15·6 g. (72%) of *di*-(2-*chloroethyl*)-2-*methoxyethylamine* (IV) as a colourless oil, b. p. 103—104°/4 mm. (Found: Cl, 35·0. $C_7H_{15}ONCl_2$ requires Cl, 35·5%); the *picrate* crystallised from dilute acetone in yellow needles, m. p. 109—110° (Found: C, 36·4; H, 4·5. $C_{13}H_{18}O_8N_4Cl_2$ requires C, 36·4; H, 4·2%). Kept overnight in methanol (5 vols.), the free base yielded NN′-*di*-(2-*chloroethyl*)-NN′-*di*-(2-*methoxyethyl*)*piperazinium dichloride*, m. p. 258° (decomp.) from dilute acetone (Found: C, 41·9; H, 7·2; N, 6·7. $C_{14}H_{30}O_2N_2Cl_4$ requires C, 42·0; H, 7·55; N, 7·0%); the *dipicrate* crystallised from dilute acetone in needles, m. p. 179—180° (Found: C, 40·2; H, 4·7. $C_{26}H_{34}O_{16}N_8Cl_2$ requires C, 39·7; H, 4·45%).

Action of Water on 2 : 2′ : 2″-Trichlorotriethylamine.—(a) *Kinetic measurements.* The freshly distilled amine (5·000 g.) was made up to 500 c.c. with water and the mixture shaken mechanically at room temperature until solution was complete (several hours). The solution was then kept at 25° while samples were withdrawn at intervals and analysed for ionic chlorine (electrometric titration with silver nitrate) and hydrochloric acid (titration with barium hydroxide using alizarin yellow). The following values are interpolated from a curve constructed from the experimental results (31 double determinations):

Time (hrs.)	20	30	40	50	70	90	140	160	190	210	240
Equiv. per mol. of (I) Cl′	1·04	1·14	1·19	1·22	1·26	1·29	1·35	1·38	1·40	1·42	1·43
Equiv. per mol. of (I) HCl	1·00	1·10	1·15	1·18	1·22	1·25	1·31	1·34	1·36	1·37	1·39

(b) *Isolation of products.* The amine was dissolved in water (100 parts by weight) by mechanical shaking for 20 hours; the resulting solution was kept at room temperature for 3 days and then treated with 0·5N-calcium picrate (582 c.c.). Several crops of picrate, some heavily contaminated with picric acid, were isolated by filtration, at once and after successive concentrations under reduced pressure, and were subjected to systematic fractional crystallisation. In this way a little of the dimer dipicrate, m. p. and mixed m. p. 222° (decomp.), was isolated from a less soluble fraction, while acidification of the combined mother liquors from the picrate of (VI), followed by removal of picric acid and evaporation, yielded 2 : 2′ : 2″-trihydroxytriethylamine hydrochloride, m. p. and mixed m. p. 179—180° after crystallisation from 80% alcohol.

The only new picrate isolated was 2-*chloroethyldi*-(2-*hydroxyethyl*)*ammonium picrate*, which crystallised from ethyl acetate–alcohol in large orange rhombs, m. p. 119° (Found: C, 36·3; H, 4·3; N, 13·7; Cl, 9·3. $C_{12}H_{17}O_9N_4Cl$ requires C, 36·3; H, 4·3; N, 14·1; Cl, 9·0%). This picrate was dissolved in water and the solution treated with excess of hydrochloric acid; after removal of picric acid by filtration, and extraction with benzene, the solution was evaporated to dryness under reduced pressure. Two crystallisations of the solid residue from anhydrous alcohol–ether yielded 2-*chloroethyldi*-(2-*hydroxyethyl*)*ammonium chloride* (VI), m. p. 93—94° (Found: C, 35·2; H, 7·1; Cl, 35·4. $C_6H_{15}O_2NCl_2$ requires C, 35·3; H, 7·35; Cl, 34·8%); heating with thionyl chloride yielded 2 : 2′ : 2″-trichlorotriethylamine hydrochloride, m. p. and mixed m. p. 134—135°. The hydrochloride (VI) (7·306 g.), dissolved in absolute alcohol, was treated with 0·385N-alcoholic sodium ethoxide (93 c.c.); the precipitated sodium chloride was filtered off and the filtrate evaporated to dryness under reduced pressure at room temperature. The solid residue, twice crystallised from 80% alcohol, yielded NNN′N′-*tetra*-(2-*hydroxyethyl*)*piperazinium dichloride* (III), m. p. 230—231° (decomp.) (Found: C, 43·0; H, 8·2; N, 8·3. $C_{12}H_{26}O_4N_2Cl_2$ requires C, 43·0; H, 8·4; N, 8·4%), identified by conversion into its picrate, m. p. and mixed m. p. with a

synthetic specimen 215—216° (Found: C, 40·3; H, 4·6; H, 15·7. Calc. for $C_{14}H_{32}O_{12}N_8$: C, 40·0; H, 4·45; N, 15·6%).

Miscellaneous Preparations.—2-Acetoxyethylamine. A mixture of 2-hydroxyethylamine (122 g.) and acetic acid (132 g.) was saturated with dry hydrogen chloride at 0° and the mixture kept at room temperature overnight. Next day excess hydrogen chloride was removed in a current of dry air and the desired hydrochloride (210 g.; 75%) precipitated with dry acetone. *2-Acetoxyethylammonium chloride* crystallises from acetone in stout needles, m. p. 130° (Found: C, 34·9; H, 6·9; N, 9·55. $C_4H_{10}O_2NCl$ requires C, 34·4; H, 7·2; N, 10·0%). This hydrochloride (98 g.) was dissolved in absolute alcohol and treated, with cooling and shaking, with sodium ethoxide from sodium (17·8 g.) and absolute alcohol (300 c.c.). Distillation of the filtrate from the precipitated sodium chloride yielded *2-acetoxyethylamine* (35·9 g.; 50%) as a viscous oil, b. p. 160—161°/4 mm., $n_D^{20°}$ 1·4716 (Found: C, 46·7; H, 8·7; N, 13·55. $C_4H_9O_2N$ requires C, 46·6; H, 8·7; N, 13·6%). No well-defined products were obtained on condensing this base with ethylene oxide or ethylene chlorohydrin.

Phthalo-2-acetoxyethylimide. Phthalo-2-hydroxyethylimide (50 g.; Wenker, *J. Amer. Chem. Soc.*, 1937, **59**, 422) was refluxed for 2 hours with acetic anhydride (30 g.); the product was poured into water and collected after for some hours. Crystallisation from dilute alcohol yielded the *acetate* (40 g.; 63%) in flattened needles, m. p. 89—90° (Found: C, 61·7; H, 4·8; N, 5·8. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%). The method of Ing and Manske (*J.*, 1926, 2348) was not successful in bringing about the fission of this compound.

2 : 2′-Diacetoxydiethylammonium chloride. The following procedure is simpler than that described by Mann (*J.*, 1934, 461). Diethanolamine was dissolved in acetic acid (2 equivs.) with cooling, and the solution was saturated with dry hydrogen chloride at 0°. Next day most of the excess of hydrogen chloride was removed under reduced pressure and the remainder by aspirating dry air through a suspension of the reaction product in dry chloroform. Filtration, followed by washing with acetone and ether, yielded the desired hydrochloride which crystallised from alcohol in large glistening plates, m. p. 146—148° (Found: C, 42·7; H, 6·8; N, 6·0. Calc. for $C_8H_{16}O_4NCl$: C, 42·6; H, 7·1; N, 6·2%). We were unable to distil the free base liberated from this hydrochloride, and no definite product could be isolated from the reaction product of the crude base and ethylene oxide.

We are indebted to the Director General of Scientific Research (Defence), Ministry of Supply, for permission to publish this paper; the microanalyses were carried out by Mr. G. Ingram.

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101. *Some Dichloroamine Derivatives.*

By L. J. LERMIT and (the late) R. C. G. MOGGRIDGE.

The dihydroxyamines (I), (II), and (III) have been prepared by the action of di- (or tri-) ethylene chlorohydrin on the appropriate amines; they have been converted by the action of thionyl chloride into the corresponding dichloroamines (V), (VI), and (VII). These compounds undergo spontaneous ring-closure to give quaternary ammonium compounds; (VI) gives a piperazinium (X) and (VII) gives a morpholinium derivative (XII), while (V) gives one of two compounds (IX or XI) according to the conditions used.

IN connection with work on methyl-2 : 2′-dichlorodiethylamine (IV) (Eisleb, *Ber.*, 1941, **74**, *B*, 1433) it was desired to have specimens of the related dichloroamines (V—VII), and the corresponding diols (I—III). In this paper the preparation and characterisation of these compounds are described.

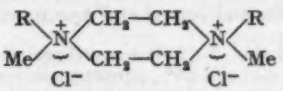
$$CHRR'\cdot CH_2\cdot NMe\cdot CH_2\cdot CH_2R''$$

I; R = O·CH$_2$·CH$_2$·OH, R′ = H, R″ = OH.
II; R = O·CH$_2$·CH$_2$·O·CH$_2$·CH$_2$·OH, R′ = H, R″ = OH.
III; R = R″ = O·CH$_2$·CH$_2$·OH, R′ = H.
IV; R = R″ = Cl, R′ = H.
V; R = O·CH$_2$·CH$_2$Cl, R′ = H, R″ = Cl.
VI; R = O·CH$_2$·CH$_2$·O·CH$_2$·CH$_2$Cl, R′ = H, R″ = Cl.
VII; R = R″ = O·CH$_2$·CH$_2$Cl, R′ = H.

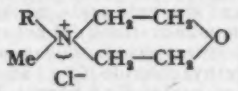
The *diols* (I—III) were prepared without difficulty by the interaction of di-(or tri-) ethylene chlorohydrin with the appropriate amine [methylamine for (III), methyl-2-hydroxyethylamine for (I) and (II)]; these reactions were carried out in the presence of either sodium carbonate or excess of amine. The products were colourless oils, miscible with water; many derivatives crystallised only with difficulty. Derivatives suitable for characterisation were the *picrolonates* (m. p. 116°, 98°, and 75° respectively) and the *picrates* of the bis-*p*-nitrobenzoates (m. p. 124°, 128°, and 109·5° respectively).

The *dichlorides* (V—VII) were prepared without difficulty by the action of thionyl chloride on the corresponding diols. All the products were colourless oils which could be identified by their *picrolonates*; their most characteristic property, however, was that of undergoing ring-closure to give the quaternary ammonium derivatives. Similar behaviour is shown by (IV) (Eisleb, *loc. cit.*), the product in this case being the piperazinium derivative (VIII) (Hanby

and Rydon, this vol., p. 513 *). The behaviour of (V) is of special interest, since it might form either the *piperazinium* derivative (IX) or the *morpholinium* derivative (XI).



VIII; R = $CH_2 \cdot CH_2Cl$.
IX; R = $CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2Cl$.
X; R = $CH_2 \cdot CH_2 \cdot [O \cdot CH_2 \cdot CH_2]_2 \cdot Cl$.



XI; R = $CH_2 \cdot CH_2Cl$.
XII; R = $CH_2 \cdot CH_2 \cdot O \cdot CH_2 \cdot CH_2Cl$.
XIII; R = $CH_2 \cdot CH_2 \cdot OH$.

Hanby and Rydon (*loc. cit.*) have in fact shown that both these compounds (IX and XI) can be formed from (V), the nature of the product depending on the conditions. Our results are essentially similar, (IX) being formed if (V) is heated alone, (XI) if (V) is dissolved in alcohol and left, either in the hot or in the cold. On leaving (V) alone at room temperature we have consistently obtained (XI), though Hanby and Rydon under these conditions obtained (IX). The two changes clearly occur with nearly equal ease, and this discrepancy is probably to be attributed to some minor difference of conditions. Hanby and Rydon have proved the structure of (XI) by synthesis from *N*-2-chloroethylmorpholine; the opportunity is taken here to describe two additional syntheses. In the first, *N*-methylmorpholine was treated directly with ethylene chloride; in the second, (XIII) was first prepared by the action of ethylene chlorohydrin on *N*-methylmorpholine, and then converted into (XI) by the action of thionyl chloride.

There is no ambiguity about the nature of the products of ring-closure of (VI) and (VII), since (VI) cannot give a morpholinium, nor (VII) a piperazinium, derivative. The products are therefore considered to be (X) and (XII) respectively; this is confirmed by the analysis of (X), and of the *picrates* and *styphnates* of both (X) and (XII). The ring-closures of the chloro-compounds (V), (VI), and (VII) proceed with considerable ease; the percentage reaction of the pure compounds after 18—19 hours at room temperature was about 14, 28, and 74% respectively.

Experimental.

The equivalents quoted were obtained by titration against N/10-sulphuric acid using methyl-red as indicator. Picrate, styphnate, and picrolonate figures were obtained by means of the "Nitron" reagent.

Methyl-2-hydroxyethyl-2-(2-hydroxyethoxy)ethylamine (I).—2-(2-Hydroxyethoxy)ethyl chloride (25 g.; Fourneau and Ribas, *Bull. Soc. chim.*, 1927, **41**, 1046) and methyl-2-hydroxyethylamine (75 g.; Knorr and Mathes, *Ber.*, 1898, **31**, 1069) were heated to 90°; reaction then took place with evolution of heat. The mixture was kept at 95—100° for 1 hour, the excess of methyl-2-hydroxyethylamine removed under reduced pressure, and the residue treated with excess of concentrated aqueous sodium hydroxide. The mixture was extracted by chloroform, the extracts were dried and concentrated, and the residue was distilled to give the required *diol* (I); 25 g., b. p. 126°/2 mm. (Found: equiv., 164. $C_7H_{17}O_3N$ requires equiv., 163). If the above reaction were carried out using sodium hydroxide solution instead of excess of amine very poor yields were obtained. The *picrolonate* had m. p. 116° after recrystallisation from alcohol–ethyl acetate (Found: picrolonic acid, 62·0. $C_{17}H_{25}O_8N_5$ requires picrolonic acid, 61·8%). The *styphnate* had m. p. 77° after recrystallisation from alcohol–ethyl acetate (Found: C, 38·4; H, 5·1; N, 13·8; styphnic acid, 60·2. $C_{13}H_{20}O_{11}N_4$ requires C, 38·2; H, 4·9; N, 13·7; styphnic acid, 60·0%).

The bis-*p*-nitrobenzoate, prepared from the diol (I) and *p*-nitrobenzoyl chloride in pyridine, was first obtained with m. p. 75°; the material changed spontaneously, however, either on standing or during recrystallisation from alcohol, into another form, m. p. 114°. That these were two forms of the same compound was shown by the fact that both gave the same *picrate*, m. p. 124° after recrystallisation from alcohol–acetone (Found: picric acid, 33·1. $C_{27}H_{26}O_{16}N_8$ requires picric acid, 33·1%).

With benzyl iodide in acetone the diol (I) gave a quaternary *iodide*; recrystallised from alcohol–ether, m. p. 82—83° (Found: I, 32·8. $C_{14}H_{24}O_3NI$ requires I, 33·3%).

With 3:5-dinitrobenzoyl chloride, triphenylmethyl chloride, methyl iodide, methyl-*p*-toluenesulphonate, α-naphthyl *iso*cyanate, or picric acid, the diol (I) gave compounds that did not crystallise.

Methyl-2-hydroxyethyl-2-{2-(2-hydroxyethoxy)ethoxy}ethylamine (II).—The fraction, b. p. 110—150°/15 mm., obtained in the preparation of 2-(2-hydroxyethoxy)ethyl chloride on redistillation yielded 2-{2-(2-hydroxyethoxy)ethoxy}ethyl chloride, b. p. 113—114°/2 mm. (Lourenco, *Ann. Chim.*, 1863, **67**, 290, gives b. p. 222—232°) (Found: Cl, 20·5. Calc. for $C_6H_{13}O_2Cl$: Cl, 21·1%). This compound (85 g.), methyl-2-hydroxyethylamine (38 g.), sodium carbonate (35 g.), and water (150 c.c.) were refluxed for 8 hours. The mixture was then cooled, and solid sodium hydroxide (*ca.* 100 g.) added gradually with cooling until sodium salts began to crystallise. The solution was then extracted with chloroform, the extract dried and concentrated, and the residue distilled to give the required *diol* (II) in 68% yield, b. p. 165—167°/2 mm. (Found: equiv., 206. $C_9H_{21}O_4N$ requires equiv., 207). Substitution of sodium hydroxide for sodium carbonate in the above reaction resulted in very low yields. The chlorohydrin and methyl-2-hydroxyethylamine reacted in the absence of solvent at 125°, but the yield of the diol (II) was only 36%. The *picrolonate* of (II), recrystallised from alcohol–ethyl acetate, had m. p. 98° (Found: picrolonic acid, 56·2. $C_{19}H_{29}O_9N_5$ requires picrolonic acid, 56·1%).

* The results of Hanby and Rydon became available to the authors at a late stage of this work. The authors wish to express their appreciation of the courtesy shown to them in this matter by Dr. Rydon.

The bis-*p*-nitrobenzoate, prepared from (II) and *p*-nitrobenzoyl chloride in pyridine, was an oil; with picric acid in acetone it gave a *picrate*, recrystallised from alcohol–acetone, m. p. 128° (Found: picric acid, 31·1. $C_{29}H_{30}O_{17}N_6$ requires picric acid, 31·0%).

With picric and styphnic acids, triphenylmethyl chloride, and benzyl and *p*-nitrobenzyl iodides, the diol (II) gave compounds which did not crystallise.

Methyldi-2-(2-hydroxyethoxy)ethylamine (III) *and Methyl-2-(2-hydroxyethoxy)ethylamine.*—2-(2-Hydroxyethoxy)ethyl chloride (62 g.) and methylamine (46 c.c. of a 35% aqueous solution) were put in a pressure bottle and heated for 8 hours; during the first 6 hours the temperature was slowly raised from 55° to 75°, during the last 2 hours from 75° to 100°. The solution was then cooled, the bottle opened, and the reaction products isolated as in the case of the diol (II). Two well-defined fractions were obtained on distillation, *viz.*: (*a*) *methyl-2-(2-hydroxyethoxy)ethylamine*, b. p. 90—91°/4·5 mm., 11% yield (Found: equiv., 121. $C_5H_{13}O_2N$ requires equiv., 119); *picrate*, m. p. 103° after recrystallisation from alcohol (Found: picric acid, 65·8. $C_{11}H_{16}O_9N_4$ requires picric acid, 65·8%). (*b*) The *diol* (III), b. p. 165°/2 mm., 55% yield (Found: equiv., 207·5. $C_9H_{21}O_4N$ requires equiv., 207). The *picrolonate*, recrystallised from ethyl acetate, had m. p. 75° (Found: picrolonic acid, 56·0. $C_{15}H_{29}O_9N_5$ requires picrolonic acid, 56·1%). The oily bis-*p*-nitrobenzoate gave a *picrate*, m. p. 109·5° after recrystallisation from alcohol–acetone (Found: picric acid, 31·0. $C_{29}H_{30}O_{17}N_6$ requires picric acid, 31·0%).

Preparation of the Dichlorides (V—VII).—The diol (I, II, or III, 0·1 g.-mol.) in dry trichloroethylene (40 c.c.) was saturated with dry hydrogen chloride; the diol hydrochloride then separated as an oil. The mixture was refluxed on the water-bath while thionyl chloride (8 c.c.) was added gradually; the mixture was then boiled till the evolution of sulphur dioxide and hydrogen chloride had almost ceased. The mixture was then cooled and extracted with water, and the extracts were treated with excess of aqueous sodium carbonate. The oily product was separated and dried (Na_2SO_4). The dichlorides (V—VII) were all unstable, and were therefore not analysed; nor were they normally distilled. In order approximately to determine their b. ps., however, small amounts were distilled in a vacuum from a flask with a short distillation passage, the flask being immersed in an oil-bath preheated to about 20° above the boiling point.

Methyl-2-chloroethyl-2-(2-chloroethoxy)ethylamine (V). This was prepared as above in 65% yield; b. p. 96—98°/3·5 mm. The *picrate*, crystallised from ethyl acetate, had m. p. 59° (Found: picric acid, 53·3. $C_{12}H_{16}O_9N_4Cl_2$ requires picric acid, 53·4%). The *picrolonate*, crystallised from ethyl acetate, had m. p. 114—115° (Found: picrolonic acid, 56·8. $C_{17}H_{23}O_8N_5Cl_2$ requires picrolonic acid, 56·9%). With benzyl iodide in acetone a quaternary *iodide* was formed; this, after recrystallisation from acetone–ether, had m. p. 96—98° (Found: I, 30·0. $C_{14}H_{22}ONCl_2I$ requires I, 30·4%).

The dichloride (V) was a colourless oil which when kept at room temperature deposited colourless crystals. An approximate idea of the rate of this change was obtained by keeping a sample in a sealed tube for 19 hours and then estimating the ionic chlorine formed. 7% of the total chlorine had become ionic, corresponding to 14% change. The nature of the crystalline product obtained from (V) depended on the conditions used, *viz.*: (*a*) *NN′-Dimethyl-NN′-di-2-(2-chloroethoxy)ethylpiperazinium dichloride* (IX; cf. Hanby and Rydon, *loc. cit.*) was obtained if (V) were kept at room temperature, alone or in alcoholic solution; if it were warmed in alcoholic solution, the ring-closure occurred with considerable evolution of heat. The compound (IX) was obtained as plates from methanol or from aqueous alcohol; it was not deliquescent, and was not molten by 240° (Found: Cl′, 17·6. $C_{14}H_{30}O_2N_2Cl_4$ requires Cl′, 17·75%). The *dipicrate*, needles from aqueous acetone, had m. p. 191° (Found: Cl, 8·93; picric acid, 58·0. $C_{26}H_{34}O_{18}N_8Cl_2$ requires Cl, 9·05; picric acid, 58·1%). On two occasions a labile form of the dipicrate was obtained, separating in needles from aqueous acetic acid, m. p. 160°; this changed spontaneously during further recrystallisation to the form, m. p. 191°. The *distyphnate*, recrystallised from aqueous acetone, had m. p. 190—195° (decomp.) (Found: styphnic acid, 59·5. $C_{26}H_{34}O_{18}N_8Cl_2$ requires styphnic acid, 59·7%).

(*b*) *N-Methyl-N-2-chloroethylmorpholinium chloride* (XI) was formed on warming (V) alone in the absence of solvent; deliquescent needles from alcohol or alcohol–ether, m. p. 175—180° (decomp.) (Found: Cl, 36·1; N, 7·4; Cl′, 17·8. $C_7H_{15}ONCl_2$ requires Cl, 35·5; N, 7·0; Cl, 17·75%). The *picrate*, recrystallised from aqueous acetone, had m. p. 170—171° (Found: picric acid, 58·0. $C_{13}H_{17}O_8N_4Cl$ requires picric acid, 58·1%). The *styphnate*, needles from alcohol–acetic acid, had m. p. 117° (Found: styphnic acid, 59·7. $C_{13}H_{17}O_9N_4Cl$ requires styphnic acid, 59·7%).

The picrate of (XI) was also synthesised as follows: (i) *N*-Methylmorpholine (1 c.c.), ethylene chlorohydrin (0·585 c.c.) and water (100 c.c.) were mixed and kept at room temperature for 5 hours; they were then heated to 100° for 1 hour, and the solution then concentrated to dryness under reduced pressure. The residual syrup was refluxed for 2 hours with dry chloroform and thionyl chloride (5 c.c.). The crystalline solid which separated was collected, dissolved in alcohol, reprecipitated by the addition of ethyl acetate, dissolved in water, and treated with aqueous picric acid. The picrate deposited had m. p. 170° after recrystallisation from aqueous acetone. (ii) *N*-Methylmorpholine (1 c.c.) in water and ethylene dichloride (0·725 c.c.) in chloroform were mixed and refluxed for 2 hours. The solvents were removed under reduced pressure, the residual syrup dissolved in water, and aqueous picric acid added. The resulting picrate had m. p. 169°. The products of both these syntheses were shown by mixed m. p. to be identical with the picrate of (XI) as prepared from the dichloride (V).

Methyl-2-chloroethyl-2-{2-(2-chloroethoxy)ethoxy}ethylamine (VI).—This, prepared from the diol (II) as above in 55% yield, had b. p. *ca.* 130°/2 mm. The *picrolonate*, from ethyl acetate–petrol, had m. p. 95—96° (Found: picrolonic acid, 48·0. $C_{19}H_{27}O_7N_5Cl_2$ requires picrolonic acid, 48·0%). With styphnic acid, flavianic acid, benzyl and *p*-nitrobenzyl iodides, and sodium tribromophenoxide the dichloride (VI) gave products which did not crystallise.

The dichloride (VI) changed on standing to the piperazinium *derivative* (X). The rate of change (estimated by formation of ionic chlorine) was *ca.* 28% in 19 hours at room temperature. The compound (X) was conveniently prepared by warming an alcoholic solution of (VI); it was recrystallised from absolute alcohol; m. p. 227° (decomp.) (Found: Cl, 29·3; N, 6·1; Cl′, 14·6. $C_{18}H_{38}O_4N_2Cl_4$ requires

Cl, 29·1; N, 5·75; Cl′, 14·55%). The *dipicrate*, from aqueous acetone, had m. p. 141—143° (Found: picric acid, 51·8. $C_{30}H_{42}O_{18}N_8Cl_2$ requires picric acid, 52·2%). The *distyphnate*, from aqueous acetone, had m. p. 169° (decomp.) (Found: styphnic acid, 53·8. $C_{30}H_{42}O_{20}N_8Cl_2$ requires styphnic acid, 53·9%).

Methyldi-2-(2-chloroethoxy)ethylamine (VII).—This, prepared from the diol (III) as above in 75% yield, had b. p. *ca.* 130°/2 mm. The *picrolonate*, from ethyl acetate–light petroleum, had m. p. 90° (Found: picrolonic acid, 48·0. $C_{19}H_{27}O_7N_9Cl_2$ requires picrolonic acid, 48·0%). This compound was even more unstable than (V) and (VI), undergoing *ca.* 74% change (judging by formation of ionic chlorine) in 18 hours at room temperature. The morpholinium compound (XII) formed was a colourless viscous liquid and was not obtained crystalline; its aqueous solution readily gave a *picrate* which, after recrystallisation from aqueous acetone, had m. p. 130—131° (Found: picric acid, 52·0. $C_{15}H_{21}O_9N_4Cl$ requires picric acid, 52·2%), and a *styphnate* which, after recrystallisation from ethyl acetate–acetic acid, had m. p. 125—127° (decomp.) (Found: styphnic acid, 54·0. $C_{15}H_{21}O_{10}N_4Cl$ requires styphnic acid, 53·9%).

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RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, July 17th*, 1946.]

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102. *The Constitution of ψ-Santonin. Part III. Some Synthetical Experiments.*

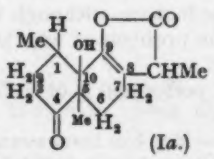
By WESLEY COCKER and CYRIL LIPMAN.

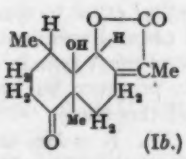
The synthesis of 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic acid* and its *lactone* is described. It is possible that the latter is identical with inactive desmotropo-ψ-santonin methyl ether. Attempts to obtain the inactive material from *d*-desmotropo-ψ-santonin have so far failed.

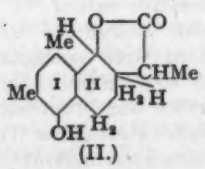
WHEN ψ-santonin (I*a* or I*b*) is treated with 55% sulphuric acid or anhydrous formic acid it undergoes dehydration and rearrangement, and a dextrorotatory desmotropo-ψ-santonin is obtained (Clemo and Cocker, Part I, *J.*, 1946, 30). Desmotropo-ψ-santonin was given the empirical formula $C_{15}H_{18}O_3$, and it was believed that its structure was best represented by (II), the isomeric compound in which the lactone is fused at position 7 being less acceptable on biogenetic grounds [cf. the structure of *l*-santonin (Clemo, Haworth, and Walton, *J.*, 1929, 2368; 1930, 1110; Clemo and Haworth, *J.*, 1930, 2570)].

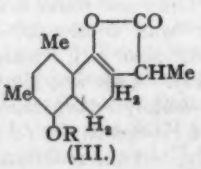
Evidence obtained since the publication of Part I of this series has led us to doubt the accuracy of the saturated structure (II) previously advanced for the desmotropo-compound. There is in fact some evidence which suggests that the butenolide structure (III; R = H) is a better representation of the compound. If this is correct its empirical formula is $C_{15}H_{16}O_3$.

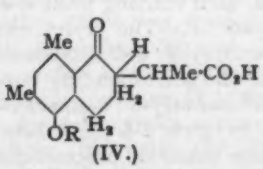
We have therefore synthesised a lactone of structure (III; R = Me) to compare with the material obtained from ψ-santonin itself with a view to proving the position at which the lactone ring in the latter is fused, and also whether desmotropo-ψ-santonin is unsaturated. We have also synthesised the *keto-acid* (IV; R = Me).


(I*a*.)


(I*b*.)


(II.)


(III.)


(IV.)

The evidence for and against the unsaturated character of the lactone ring is as follows. When desmotropo-ψ-santonin is methylated in alkaline solution and the mixture is acidified and heated for several minutes the dextrorotatory methyl ether described by Clemo and Cocker (*loc. cit.*) is obtained in good yield, and this compound is undoubtedly a lactone. However, if

the alkaline solution is carefully neutralised in the cold, another dextrorotatory methyl ether is obtained which dissolves with effervescence in sodium carbonate solution. Moreover, the former methyl ether can by converted, by alkaline hydrolysis and careful neutralisation, into the same acid. This acid may be a mixture of enantiomorphic forms but by crystallisation a highly crystalline acid is obtained which is stable at ordinary temperatures, but when heated above its melting point or refluxed with acetic anhydride rapidly loses water and yields the lactone previously described. Similarly desmotropo-ψ-santonin itself may be hydrolysed to an acid which is reconverted to desmotropo-ψ-santonin on heating above its melting point. The stability of these acids towards mineral acid and the fact that they can be lactonised only under energetic conditions appears to indicate that they are keto-acids.

On the other hand we have, so far, been unable to obtain ketone derivatives from the acids obtained from either desmotropo-ψ-santonin or its methyl ether, but this is not necessarily evidence that the keto-group is absent since we have also been unable to obtain evidence of carbonyl activity in the synthetic *1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid* where the keto-group is " protected ". Similar experiences were encountered by Cagniant and Buu-Hoï (*Bull. Soc. chim.*, 1942, **9**, 841) who had the greatest difficulty in obtaining carbonyl activity in 1-keto-2-ethyl-7-*tert.*-butyl-1 : 2 : 3 : 4-tetrahydronaphthalene and found none in 1-keto-6-methoxy-5-methyl-2-ethyl-8-*iso*propyl-1 : 2 : 3 : 4-tetrahydronaphthalene. In fact it may be that the absence of carbonyl activity indicates the presence of the C=O group at 9 rather than at 7 in the acids under discussion, and hence for the fusion of the lactone ring at 9 rather than at 7.

Furthermore, we have been unable to oxidise either desmotropo-ψ-santonin or its methyl ether either with bromine and sodium hydroxide in presence of magnesium sulphate or with potassium permanganate, both of which methods have given good results in our hands when applied to the oxidation of the lactone of 2-hydroxy*cyclo*hexyl-α-*iso*butyric acid. By both methods 2-keto*cyclo*hexyl-α-*iso*butyric acid was obtained in good yields.* Alexander, Charlesworth, and McCrae (*Canadian J. Res.*, 1943, **21**, *B*, 1) also found these reagents successful in the oxidation of the lactone of 2-hydroxy*cyclo*hexylacetic acid.

If the above results are taken to mean that the lactones are unsaturated contrary evidence is provided by the fact that we have so far failed to reduce desmotropo-ψ-santonin either with sodium in alcohol (cf. Part I, p. 36) or with sodium amalgam in alcohol (cf. Clemo, Haworth, and Walton, *J.*, 1930, 1110).

All efforts to racemise desmotropo-ψ-santonin or its methyl ether or the acids derived from these compounds have failed, although they were subjected for long periods to the action of boiling pyridine, aqueous and alcoholic potash, and acetic anhydride. This failure to racemise is not difficult to explain if the lactones are saturated, but, if they are unsaturated, autoracemisation would be expected to take place, especially if they were of the αβ type since racemisation would then be immediate on hydrolysis to the corresponding keto-acid. Racemisation would, however, be more difficult if the lactones were of the βγ type, and this structure is not impossible in view of the possible conjugation of the butenolide double bond with the aromatic system.

We have, therefore, as yet been unable to obtain an inactive specimen of desmotropo-ψ-santonin or its methyl ether to compare with the synthetic lactone, although the properties of the synthetic and natural specimens are very similar. The problem of whether the lactone is or is not unsaturated must remain open for the time being.

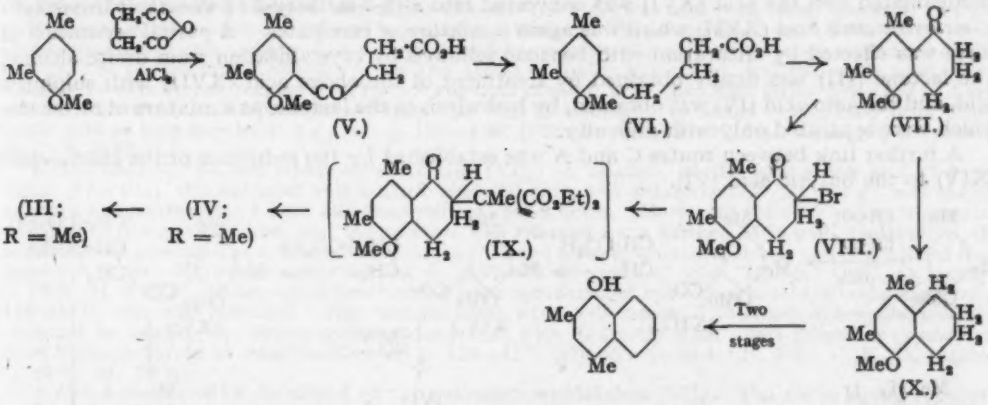
More work is in progress, but we feel that that already performed is of sufficient interest to warrant a report at this stage.

The keto-acid (IV; R = Me) and its lactone (III; R = Me) has been synthesised by three routes, each starting from *m*-4-xylenol. Only one route is of real preparative value.

Route A.—The xylyl methyl ether was condensed with succinic anhydride to give β-(*2-methoxy-3 : 5-dimethylbenzoyl*)*propionic acid* (V) which was reduced with amalgamated zinc to the corresponding butyric *acid* (VI). This was ring-closed with 80% sulphuric acid to *1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (VII) which was brominated in ether to give *2-bromo-1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (VIII). All these reactions proceeded satisfactorily, but the reaction of ethyl sodiomethylmalonate with (VIII) was very inefficient and most of the bromo-ketone was recovered unchanged. Only small quantities of the keto-acid (IV; R = Me) were obtained, but it was identical with the material produced by the alternative routes. The yield of (IV) was only slightly improved by the use of ethyl potassiomethylmalonate even when the reaction was performed in boiling

* Unpublished work to be communicated shortly in Part IV of this series.

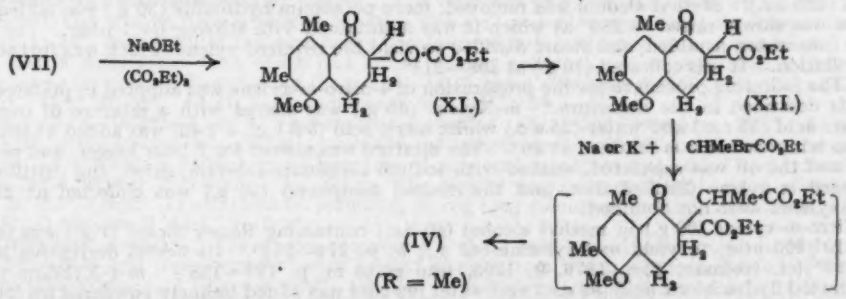
xylene. It appears that the bromine in (VIII) is only feebly reactive, a fact that was confirmed by its slow rate of hydrolysis with boiling alkali.



All attempts to isolate the malonic ester (IX) were unsuccessful. Even in the molecular still it apparently decomposed and it was therefore directly hydrolysed to (IV; R = Me) with alcoholic potash.

The orientation of the substituents in compounds (V) to (VII) was proved by the fact that (VII) was readily reduced by amalgamated zinc to *5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene* (X) which was dehydrogenated and demethylated to give 2 : 4-dimethyl-1-naphthol (Cornforth, Cornforth, and Robinson, *J.*, 1943, 168; Clemo and Cocker, *loc. cit.*).

Route B.—The tetralone (VII) was condensed with ethyl oxalate in presence of sodium ethoxide to give *ethyl 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-glyoxylate* (XI) which was heated with powdered glass to give good yields of *ethyl 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-carboxylate* (XII). The sodio-derivative, and later the potassio-derivative, was then condensed in boiling xylene with ethyl-α-bromopropionate (cf. B.P. 341,402 for a similar preparation of desmotropo-santonin). A large proportion of the starting materials was recovered unchanged, but small amounts of a thick red oil were isolated which on hydrolysis with alcoholic potash yielded traces of the required keto-acid (IV; R = Me).

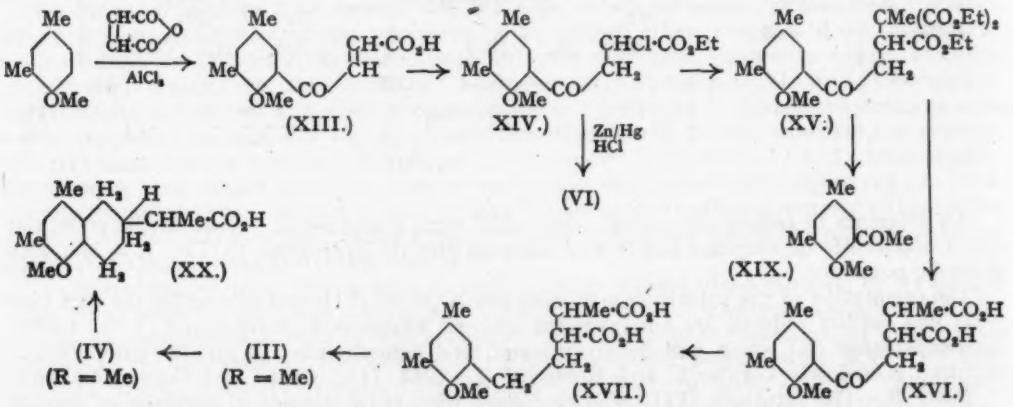


In view of the poor yields obtained in the conversion of (XII) into (IV) this route was abandoned.

Route C.—This was similar to the method used by Clemo, Haworth, and Walton (*J.*, 1929, 2368) for the synthesis of desmotroposantonin. *m*-4-Xylyl methyl ether was condensed in ligroin with maleic anhydride to give *β-(2-methoxy-3 : 5-dimethylbenzoyl)acrylic acid* (XIII). This was condensed with hydrogen chloride in alcohol at 0° to give *ethyl α-chloro-β-(2-methoxy-3 : 5-dimethylbenzoyl)propionate* (XIV). The direction of addition of the hydrogen chloride must obviously be in the manner stated since the final stage of the synthesis yields a compound identical with that obtained from routes A and B (compare Clemo, Haworth, and Walton, *loc. cit.*). The chloro-ester was then condensed with ethyl sodiomethylmalonate to give *ethyl α-(2-methoxy-3 : 5-dimethylbenzoyl)butane-βγ-tricarboxylate* (XV). This was hydrolysed with alcoholic potash and gave *α-(2-methoxy-3 : 5-dimethylbenzoyl)butane-βγ-dicarboxylic acid* (XVI) as a mixture of racemates of which at least a partial separation was effected by crystallisation first from ligroin and then from water. During the alkaline hydrolysis a neutral compound

was produced which was shown to be identical with **2-*methoxy*-3 : 5-*dimethylacetophenone*** (XIX) prepared directly from *m*-4-xylyl methyl ether and acetic anhydride. On reduction with amalgamated zinc the acid (XVI) was converted into **α-(β-2-*methoxy*-3 : 5-*dimethylphenylethyl*)-α'-*methylsuccinic acid*** (XVII) which was again a mixture of racemates. A partial separation of these was effected by trituration with benzene followed by crystallisation from dilute alcohol. The lactone (III) was finally obtained by treatment of the above acid (XVII) with sulphuric acid, and the keto-acid (IV) was obtained, by hydrolysis of the lactone, as a mixture of racemates which were separated only with difficulty.

A further link between routes C and A was established by the reduction of the chloro-ester (XIV) to the butyric acid (VI).



The keto-acid (IV; R = Me) was reduced by amalgamated zinc to a mixture of acidic substances (XX) which probably corresponded to a mixture of racemates of ψ-santonous acid methyl ether, but the yield was too small to effect a purification.

Experimental.

m-4-*Xylenol*.—(*a*) *m*-Xylene-4-sulphonyl chloride (Ullmann, *Ber.*, 1909, **42**, 2057; Pollak and Lustig, *Annalen*, 1923, **433**, 199) (50 g.) was refluxed for 6 hours with potassium hydroxide (50 g.) in methyl alcohol (150 c.c.). Methyl alcohol was removed, more potassium hydroxide (30 g.) was added, and the mixture was slowly raised to 280° at which it was maintained with stirring for 1 hour. The melt was poured into water, acidified, and steam distilled to yield the required xylenol which was further purified by distillation. It was collected (10 g.) at 208—211°.

(*b*) The following procedure for the preparation of 4-nitro-*m*-xylene was adopted in preference to the methods described in the literature.* *m*-Xylene (50 g.) was stirred with a mixture of concentrated sulphuric acid (55 c.c.) and water (25 c.c.) whilst nitric acid (3·6 c.c., *d* 1·42) was added at such a speed that the temperature was retained at 20°. The mixture was stirred for 1 hour longer, and poured into water, and the oil was separated, washed with sodium carbonate solution, dried, and distilled. Some unchanged *m*-xylene distilled first, and the desired compound (30 g.) was collected at 235—240°. Dinitroxylenes were not obtained.

4-Nitro-*m*-xylene (60 g.) in methyl alcohol (40 c.c.) containing Raney nickel (1 g.) was reduced at 100—110°/100 atm. to yield *m*-4-xylidine (43 g.), b. p. 214—216°. Its acetyl derivative had m. p. 125—126° (cf. Hofman, *Ber.*, 1876, **9**, 1295, who gives m. p. 127—128°). *m*-4-Xylidine (33 g.) in concentrated hydrochloric acid (99 c.c.) and water (99 c.c.) was added to finely powdered ice (500 g.) and the stirred mixture was kept at − 5° whilst a concentrated solution of sodium nitrite (24·5 g.) was added over ½ hour. Stirring was continued at − 5° for a further ½ hour and the solution was then added dropwise to a boiling solution of hydrated copper sulphate (11 g.) in 50% sulphuric acid (46 g.), the xylenol being removed by steam as it was produced. The aqueous distillate was extracted with ether yielding the xylenol (14 g.), b. p. 210—214°.

(*c*) A mixture containing approximately equal quantities of *p*-xylenol and *m*-4-xylenol which distilled at 205—215° was obtained from Messrs. R. Graesser, Ltd. Attempts to separate the xylenols through their sulphonic acids (cf. Brüchner, *Z. anal. Chem.*, 1928, **75**, 289) were not uniformly successful and were abandoned in favour of the following method. The mixture was cooled in ice and salt, and seeded with a crystal of *p*-xylenol, and after ½ hour the mass of crystals was collected at the pump on an ice-cold filter and thoroughly pressed. The filtrate, rich in *m*-4-xylenol, then had a setting point of 8·7° (pure *m*-4-xylenol melts at 25°), but it was considered to be sufficiently pure for further work. Bromination by the method of Francis and Hill (*J. Amer. Chem. Soc.*, 1942, **46**, 2503) gave an uptake of 1·16 atoms of bromine per mol. of xylenol, indicating the presence of 16% of *p*-xylenol.

1-*Keto*-5-*methoxy*-6 : 8-*dimethy*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic Acid and its Lactone*.—*Route A*. **β-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*propionic acid*** (V). *m*-4-Xylenol (63 g.) was methylated

* We are indebted to Mr. S. Hornsby, B.Sc., for this preparation.

by methyl sulphate (140 g.) in excess of sodium hydroxide solution, and the methyl ether (45 g.) was collected at 188—191°.

A mixture of this ether (17·4 g.), succinic anhydride (13·0 g.) and dry benzene (50 c.c.) was stirred vigorously, and finely powdered aluminium chloride (18·0 g.) was added in small portions. In the early stages of the addition a gel was repeatedly produced. This was stirred until fluid before more aluminium chloride was added. The addition took 3 hours, after which the mixture was stirred overnight. It was then poured into a mixture of ice and excess of hydrochloric acid, and the white solid which separated was collected, washed with further amounts of dilute acid, then with water, dissolved in dilute sodium carbonate, and reprecipitated from the filtered solution. It finally crystallised from dilute acetic acid as long needles (7·4 g.), m. p. 129—130° (Found: C, 65·9; H, 6·6. $C_{12}H_{16}O_4$ requires C, 66·1; H, 6·8%).

γ-(2-Methoxy-3 : 5-dimethylphenyl)butyric acid (VI). A mixture of the above *keto-acid* (7·4 g.), water (37·5 c.c.), concentrated hydrochloric acid (50 c.c.), and amalgamated zinc (50 g.) was shaken at room temperature for 1 hour and then refluxed for 8 hours. More acid (25 c.c.) and amalgamated zinc (25 g.) were then added and the mixture was refluxed for a further 16 hours. On cooling, the required *acid* separated as a cake on the surface. It was collected, washed, dried, and crystallised from ligroin (b. p. 60—80°) as colourless needles, m. p. 92—93° (Found: C, 70·0; H, 7·9. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). In one experiment, using more concentrated hydrochloric acid, a compound, m. p. 116—117°, was also obtained. This was identical with *γ-(2-hydroxy-3 : 5-dimethylphenyl)butyric acid* obtained by heating the above methoxy-compound with hydriodic acid. This substance crystallised from benzene–ligroin as small needles, m. p. 116—117° (Found: C, 69·1; H, 7·6. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

1-Keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VII). The above methoxybutyric acid (4 g.) was heated on the water-bath for 2 hours with a mixture of concentrated sulphuric acid (16·4 c.c.) and water (8 c.c.). After being poured into water, the mixture was extracted with ether, and the ethereal solution was washed with sodium carbonate, dried, and fractionated. The required *ketone* (2·0 g.) was collected at 170°/3 mm. It solidified on standing and was crystallised from ligroin (b. p. 40—60°) as colourless plates, m. p. 61·5—62° (Found: C, 76·0; H, 7·45; OMe, 14·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8; OMe, 15·2%). Its *semicarbazone* crystallised from alcohol as needles, m. p. 192—193° (Found: C, 63·9; H, 7·2. $C_{14}H_{19}O_2N_3$ requires C, 64·4; H, 7·3%). Its *2 : 4-dinitrophenylhydrazone* crystallised from benzene–alcohol as scarlet needles with a violet reflex, m. p. 204° (Found: C, 59·5; H, 5·0. $C_{19}H_{20}O_5N_4$ requires C, 59·4; H, 5·2%). Its *2-piperonylidene* derivative prepared in alcoholic sodium hydroxide crystallised from dilute alcohol in canary yellow prisms, m. p. 132—133° (Found: C, 74·0; H, 5·7. $C_{21}H_{20}O_4$ requires C, 75·0; H, 5·9%).

5-Hydroxy-1-keto-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene. The methoxytetralone (1 g.) was gently refluxed with hydriodic acid (15 c.c., *d* 1·7) for 2 hours and the mixture was poured into water, extracted with ether, and the extract washed with sodium hydrogen sulphite solution. From the ether a pale yellow solid was obtained which crystallised from ligroin (charcoal) as colourless needles, m. p. 145°, which on methylation gave the methyl ether (VII).

2-Bromo-1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (VIII). The tetralone (VII) was brominated (*a*) in carbon disulphide, (*b*) in acetic acid (cf. Bergs, *Ber.*, 1930, **63**, 1292), (*c*) in carbon tetrachloride, and (*d*) in ether (cf. Wilds, *J. Amer. Chem. Soc.*, 1942, **64**, 1424). Method (*d*) gave the best results and was performed as follows. The tetralone (2 g.) in anhydrous ether (20 c.c.) was cooled, stirred, and treated drop-wise with bromine (0·5 c.c.) at such a speed that the temperature was maintained at 10°, each drop of bromine being decolourised before the addition of the next. After a further 1 hour's stirring the solid which had separated was collected and washed with a little ether; the *bromo-ketone* crystallised from ligroin (b. p. 100—120°) as colourless needles (1·75 g.), m. p. 140—141° (Found: C, 54·5; H, 5·2. $C_{13}H_{15}O_2Br$ requires C, 55·1; H, 5·3%).

5-Methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene (X). The tetralone (VII, 5 g.) was refluxed with amalgamated zinc (25 g.), concentrated hydrochloric acid (25 c.c.), and water (16 c.c.) for 8 hours, after which a further equal quantity of acid and amalgam was added and refluxing was continued for a further 16 hours. On cooling, the *tetralin* was extracted with ether, distilled, and collected at 128°/3 mm. It solidified on standing, giving long colourless needles (Found: C, 81·7; H, 9·4. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

2 : 4-Dimethyl-1-naphthol. The above compound (1·0 g.) was heated with selenium (0·7 g.) for 4 hours at 300—350° and then extracted with methyl alcohol from which a pale yellow oil (0·2 g.) b. p. 140/3 mm. was obtained. This was gently refluxed with hydriodic acid (2 c.c., *d* 1·7) for 90 minutes, and then poured into water. The required naphthol was extracted with ether which was washed with sodium hydrogen sulphite. On removal of the ether a solid, m. p. 79—84°, was obtained which crystallised from ligroin (b. p. 80—100°) as colourless needles, m. p. 84° (cf. Cornforth, Cornforth, and Robinson, *loc. cit.*). Its picrate crystallised from aqueous alcohol and had m. p. and mixed m. p. with authentic material 143—144°.

Condensation of the bromo-ketone (VIII) *with ethyl methylmalonate.* Ethyl methylmalonate (4·7 g.) was added slowly to a stirred suspension of powdered potassium in dry benzene (30 c.c.), and the mixture was heated and stirred until all potassium had dissolved. The bromo-ketone (5 g.) in benzene (20 c.c.) was slowly added, and the mixture was stirred and refluxed for 10 hours after which it was poured into water and the benzene layer was separated, washed with water, and dried. Benzene and excess of ethyl methylmalonate were removed under reduced pressure. Since the residue appeared to decompose even in a molecular still, it was refluxed for 3 hours with potassium hydroxide (4 g.) in methyl alcohol (70 c.c.) and water (10 c.c.). Methyl alcohol was then removed under reduced pressure and the residue was poured into water, filtered (charcoal), and acidified. The reddish oil which separated was extracted with ether and the required acid was extracted from the ethereal solution with dilute aqueous sodium carbonate. The alkaline extract was filtered and acidified; a red solid (0·7 g.), m. p. 95—98°, was thus obtained. It gave no depression of m. p. with the crude 1-keto-5-methoxy-6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydronaphthalene-2-α-propionic acid (IV; R = Me) prepared by Routes B and C described below.

Route B. Ethyl 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*glyoxylate* (XI). The tetralone (VII; 10·2 g.) was dissolved in freshly distilled ethyl oxalate (7·1 g.) and cooled to − 5°. Sodium ethoxide [from sodium (1·15 g.) and alcohol (20 c.c.)] was cooled to 0° and added slowly with stirring to the above mixture, the temperature being kept at − 5—0°. A violet solution was obtained which was kept in a slowly melting ice-bath and finally at room temperature for 24 hours. The solid product was then poured into ice-water and acidified to give an oil which rapidly solidified, and was collected, washed, and dried. It crystallised from alcohol as red-yellow needles (2·5 g.), m. p. 92—94°, and was then considered sufficiently pure for further work. A sample for analysis, recrystallised from alcohol, had m. p. 93—94° (Found: C, 66·9; H, 6·6. $C_{17}H_{20}O_5$ requires C, 67·1; H, 6·6%).

Ethyl 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-*carboxylate* (XII). A mixture of the above *glyoxylate* (2·4 g.) and finely powdered glass (2·4 g.) was heated in an oil-bath at 190—195° for 2 hours. On cooling, the mixture was extracted with ether from which the required *compound* was obtained. It crystallised from ligroin (b. p. 60—80°) as silky needles (2 g.), m. p. 100—101°. In alcohol it gave a violet colouration with ferric chloride (Found: C, 69·0; H, 7·2. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2%).

Condensation with ethyl α-bromopropionate. The carbethoxy-compound was recovered unchanged when its sodio-derivative was refluxed in alcohol with excess of ethyl α-bromopropionate for 24 hours. A little of the required propionic acid (IV; R = Me) was, however, obtained as follows. The carbethoxy-compound (1·4 g.) was slowly added with stirring to finely powdered potassium (0·21 g.) in xylene (20 c.c.) and the mixture was stirred and refluxed for 3½ hours. Ethyl α-bromopropionate (1·4 g.) in xylene (10 c.c.) was then added slowly, and stirring and refluxing were continued for 30 hours. The yellow solution was then poured into water, the xylene layer was separated and dried, and the solvent was removed under reduced pressure. The gummy residue, which still gave a faint enol reaction with ferric chloride, was hydrolysed for 2 hours with a mixture of potassium hydroxide (1 g.), methyl alcohol (15 c.c.), and water (5 c.c.). The mixture was concentrated under reduced pressure, diluted, and filtered (charcoal). On acidification with dilute acetic acid a gum was obtained which after being dissolved in sodium carbonate solution, filtered, and re-acidified, gave a semi-solid product which solidified on rubbing with ligroin. It then had m. p. 80—90° and behaved in a similar manner to the mixture of racemates obtained by routes A and C. After many crystallisations from dilute alcohol it had m. p. 138—140°.

Route C. β-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*acrylic acid* (XIII). A mixture of *m*-4-xylyl methyl ether (23 g.), maleic anhydride (17 g.) and ligroin (b. p. 80—100°; 100 c.c.) was stirred and slowly treated with finely powdered aluminium chloride (23 g.). The deep red syrup was then agitated at room temperature overnight. It was poured into ice and hydrochloric acid, and the yellow solid was collected, washed with more acid, then with water, and dried; it then crystallised from dilute acetic acid as very pale yellow needles (3·5 g.), m. p. 144—145° (Found: C, 67·2; H, 6·2. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

Ethyl α-chloro-β-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*propionate* (XIV). A solution of the *acid* (XIII; 7 g.) in absolute alcohol (30 c.c.) was saturated at 0° with hydrogen chloride and then kept in a stoppered bottle for 12 hours. The deposited solid was collected, washed with a little absolute alcohol, and crystallised from ligroin (b. p. 80—100°), from which it separated as colourless prisms (6·0 g.), m. p. 88—89° (Found: C, 60·7; H, 6·6. $C_{15}H_{19}O_4Cl$ requires C, 60·3; H, 6·4%). This substance did not depress the m. p. (91—92°) of ethyl α-chloro-β-(4-methoxy-2 : 5-dimethylbenzoyl)propionate (Clemo, Haworth, and Walton, *J.*, 1929, 2383), but the identity of the new *ester* was verified by reduction with amalgamated zinc to γ-(2-methoxy-3 : 5-dimethylphenyl)butyric acid (VI), m. p. and mixed m. p. 92—93°.

Ethyl α-(2-*methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*tricarboxylate* (XV). Ethyl methylmalonate (2·5 g.) was slowly added to a stirred suspension of powdered sodium (0·4 g.) in benzene (35 c.c.), and the stirred mixture was refluxed for 1½ hours. Then the above chloro-compound (XIV; 4·1 g.) in benzene (10 c.c.) was slowly added in the cold, and the reaction was completed by refluxing for 3½ hours. Water was added to the mixture, the benzene layer was separated, and the aqueous layer was extracted twice with benzene. The combined extracts were dried and evaporated under reduced pressure, and the gummy residue was rubbed with ligroin (b. p. 40—60°), whereby it rapidly became crystalline (2·3 g., m. p. 93—95°). It crystallised from ligroin (b. p. 80—100°) as colourless prisms, m. p. 96—97° (Found: C, 63·6; H, 7·5. $C_{22}H_{32}O_8$ requires C, 63·3; H, 7·3%).

α-(2-*Methoxy*-3 : 5-*dimethylbenzoyl*)*butane*-βγ-*dicarboxylic acid* (XVI). A mixture of the above *ester* (XV; 1·5 g.), methyl alcohol (15 c.c.), and potassium hydroxide (3 g.) was refluxed for 2½ hours. The deep red solution was then diluted with water, and methyl alcohol was distilled off. On cooling, the precipitated solid (XIX; 0·25 g.) was collected and the filtrate acidified and extracted with ether. After being dried, the extract yielded an oil which slowly solidified (1·1 g.); m. p. 125—135°. This was undoubtedly a mixture of racemates. However, on trituration with a mixture of ether and ligroin it gave a solid which crystallised from water (charcoal) in colourless leaflets, m. p. 157—162° (Found: C, 61·8; H, 6·6. $C_{16}H_{20}O_6$ requires C, 62·3; H, 6·5%). The solid (XIX) obtained above was crystallised thrice from ligroin (b. p. 40—60°), and so obtained as colourless needles, m. p. 75—76° (Found: C, 74·4; H, 8·2. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%). Its *semicarbazone* crystallised from dilute alcohol as prisms, m. p. 200° (Found: C, 61·4; H, 7·3. $C_{12}H_{17}O_3N_3$ requires C, 61·3; H, 7·2%). The ketone (XIX) proved to be identical with 2-*methoxy*-3 : 5-*dimethylacetophenone* prepared directly as follows. A mixture of *m*-4-xylyl methyl ether (4 g.), ligroin (12 c.c.), and acetic anhydride (4 g.) was slowly treated with powdered aluminium chloride (5 g.). The mixture was gently warmed and then kept at room temperature for 3 hours. It was then decomposed with ice and hydrochloric acid, and extracted with ether. The extract was dried and distilled, to yield a yellow oil, b. p. 145°/1 mm., which slowly solidified. The solid crystallised from a very small quantity of ligroin (b. p. 40—60°) as colourless needles, m. p. and mixed m. p. 74—75°.

α-(β-2-*Methoxy*-3 : 5-*dimethylphenylethyl*)-α′-*methylsuccinic acid* (XVII). The above *dicarboxylic acid* (XVI; 2·25 g.) was refluxed for 15 hours with a mixture of hydrochloric acid (50 c.c.) and amalgamated zinc (50 g.). The mixture was then cooled, diluted, and extracted with ether from which

a yellow oil was obtained. This solidified on standing, and was stirred with benzene; it then had m. p. 154—160°. Crystallisation from dilute alcohol yielded small prisms (0·3 g.), m. p. 170—172° (Found: C, 64·9; H, 7·4. $C_{16}H_{22}O_5$ requires C, 65·3; H, 7·5%). The crude acid was undoubtedly a mixture of racemates.

Lactone of 1-*keto*-5-*methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-2-α-*propionic acid* (III; R = Me). The above succinic acid (XVII; 0·3 g.) was dissolved in concentrated sulphuric acid (5 c.c.) and heated for 3 minutes at 80°. After being cooled, the mixture was added to ice-water and the solid was collected, stirred with sodium bicarbonate solution, collected again, and crystallised from dilute alcohol; the *lactone* formed slender needles (0·2 g.), m. p. 159—160° (Found: C, 74·4; H, 6·9. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

0·20 G. of the lactone was boiled with 20 c.c. of 3N-sodium hydroxide until a clear solution was obtained (35 minutes). The solution was boiled with charcoal, cooled, filtered, and carefully acidified in the cold. A gum was obtained—a mixture of racemates—but this solidified overnight. It was extracted with sodium carbonate solution and filtered, and the filtrate was again acidified. The gummy material obtained was separated, desiccated, and rubbed with benzene–ligroin; a crystalline substance, m. p. 105—107°, was thereby obtained. After many recrystallisations a mixture, m. p. 134—138°, was obtained, but the yield was very small.

5-*Methoxy*-6 : 8-*dimethyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*-α-*propionic acid* (XX).—The above keto-acid was reduced for 15 hours with amalgamated zinc and hydrochloric acid, and the mixture was extracted with ether. The oil obtained from the dried extract was stirred with ligroin (b. p. 40—60°). Colourless leaflets, m. p. 57—63°, were thereby obtained, but this mixture of racemates was insufficient for further purification.

Desmotropo-ψ-santonin Methyl Ether.—This was obtained by shaking desmotropo-ψ-santonin, in excess of hot sodium hydroxide solution, with methyl sulphate. The hot solution was filtered, immediately acidified with hot concentrated hydrochloric acid, and heated on the water-bath for a few minutes. The methyl ether was then obtained from dilute alcohol as silvery needles, m. p. 159—160° (cf. Clemo and Cocker, *loc. cit.*), $[\alpha]_D^{18°}$ + 61·3° (*c*, 2·092 in glacial acetic acid) (Found: C, 74·4; H, 7·5. Calc. for $C_{16}H_{18}O_3$: C, 74·4; H, 7·0%).

Hydrolysis of Desmotropo-ψ-santonin Methyl Ether.—The lactone (0·1 g.) was heated with 2N-sodium hydroxide (10 c.c.) until it dissolved. The mixture was filtered and acidified in the cold, and the solid which separated was extracted with cold 10% sodium carbonate from which the *keto-acid* was obtained by acidification in the cold. It was crystallised several times from dilute alcohol and obtained as colourless needles, m. p. 141—142°, $[\alpha]_D^{18°}$ + 108·5° (*c*, 1·518 in pyridine) (Found: C, 69·7; H, 7·8. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·2. $C_{16}H_{22}O_4$ requires C, 69·0; H, 7·9%). Prolonged boiling of the pyridine solution did not measurably reduce the specific rotation. The acid forms a somewhat sparingly soluble sodium salt.

Re-lactonisation. The above acid was heated at 190—200° for 10 minutes, cooled, and extracted with cold dilute sodium carbonate in which most of the product was insoluble. The residue was crystallised from dilute alcohol; it then had m. p. 157·5—158°, not depressed on admixture with desmotropo-ψ-santonin methyl ether.

Hydrolysis of Desmotropo-ψ-santonin.—This substance (Clemo and Cocker, *loc. cit.*) was hydrolysed with 2N-sodium hydroxide and the product isolated in the same way as its methyl ether. The keto-acid crystallised from dilute alcohol as colourless needles, m. p. 229—230°. It was reconverted into desmotropo-ψ-santonin on heating at its m. p. for 10 minutes.

One of us (C. L.) thanks the Council of King's College for the award of a post-graduate Scholarship.

UNIVERSITY OF DURHAM,
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[*Received, July 23rd,* 1946.

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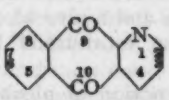
103. *The Chemistry of* 1-*Azanthraquinone. Part II. Sulphonation of* 1-*Azanthraquinone.*

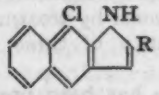
By G. R. CLEMO and N. LEGG.

1-Azanthraquinone has been sulphonated to give the 5-, 7-, and 8-monosulphonic acids. These were orientated by conversion into the chloro-1-azanthraquinones. 3-, 5-, and 6-*Chloro*-1-*azanthraquinones* have been synthesised, and the identity of 7- and 8-*chloro*-1-*azanthraquinones* established by degradation. The nitration and the action of methanolic potassium hydroxide solution on some chloro-1-azanthraquinones is described.

1-AZANTHRAQUINONE (I) (E.P. 427,485) was sulphonated by 20% oleum at 150°, with and without a mercury catalyst (F.P. 746,689; D.R.-P. 597,833), and in each case a monosulphonic



(I.)



(II, R = H.) (III, R = CO_2Et.)

acid was isolated. These on treatment with potassium chlorate and hydrochloric acid gave isomeric chloro-1-azanthraquinones. It was therefore deduced that the addition of mercury

had an appreciable effect on the sulphonation. Anthraquinone is sulphonated chiefly in the 1-position when a mercury salt is present, whereas 2-sulphonation occurs in its absence (Fierz-David, *Helv. Chim. Acta*, 1927, **10**, 197).

Since the two patents cited gave few details for the sulphonation of 1-azanthraquinone, experiments were carried out to find the best conditions for the process. The methods finally used were sulphonation with: (1) 65% oleum, with a mercury catalyst at 95°; (2) 20% oleum and a mercury catalyst at 150°; (3) 20% oleum at 145°; (4) sulphur trioxide at 170° (Schwenk, *Z. angew. Chem.*, 1931, **44**, 912).

Other methods of sulphonation which were unsuccessfully tried were the use of chlorosulphonic acid at 250° and of pyridine anhydrosulphate (Baumgarten, *Ber.*, 1926, **59**, 1976). Attempts to sulphonate 1-azanthraquinone by passing nitrogen containing sulphur trioxide vapour through a boiling decalin solution led only to the formation of a decalinsulphonic acid (characterised as its *benzyl-ψ-thiouronium* salt).

1-Azanthraquinone was therefore sulphonated by the four methods listed, and the mixed barium salts isolated as usual. The mixture, in each case, was fractionally recrystallised from water and, except in method (3), three isomeric monosulphonates were obtained and characterised as the 5-, 7-, and 8-*isomers*. In addition, a very soluble fraction was obtained in each case, which is probably a mixture of barium hydroxy-1-azanthraquinonesulphonates (referred to as " BaV "). It was pink and readily soluble in water, the colour of the solution being increased by addition of alkali but discharged by acid. It gave no lakes with aluminium or chromium salts, absorbed bromine, and gave only an oily *p*-chlorobenzyl-ψ-thiouronate, facts which indicate a mixture of monohydroxy-1-azanthraquinonesulphonic acids (cf. Houben, " Das Anthracen und die Anthrachinone," 1929, p. 402).

The following table gives the yields of isomers obtained by each method of sulphonation.

Isomer.	Method. 1.	2.	3.	4.	M. p. of chloro-deriv.
8-Sulphonate, %	33·2	31·0	27·1	21·7	217—219°
5-Sulphonate, %	28·7	13·3	nil	13·0	241—242
7-Sulphonate, %	12·8	18·7	9·6	34·8	230—231
" BaV ", %	7·9	13·8	50·1	13·8	—
Loss in working up, %	17·3	23·2	13·2	17·4	—

Owing to the appreciable loss involved in each separation it was not possible to draw any final conclusions as to the effect of the mercury as a catalyst. The yields of " α " isomers (5- +8-sulphonates) was lower when no mercury was present, but the yield of " β "-isomers (7-sulphonate) fell in method 3 in which no mercury was added, although in method 4 it was very much higher than in the catalytic sulphonations.

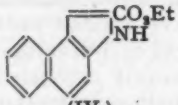
The non-detection of the 6-sulphonic acid was rather surprising, but this might be due to its being formed to such a small extent that it was lost in the working up. Attempts to prepare the 6-sulphonic acid by the action of sodium sulphite solution on 6-bromo-1-azanthraquinone (cf. Schmidt, *Ber.*, 1904, **37**, 66) failed, although the bromine was removed and an acid formed, which gave a *p*-chlorobenzyl-ψ-thiouronate, but the analytical data did not agree with the values required. Attempts to repeat this experiment gave inconsistent results.

1-Azanthraquinone resembles anthraquinone-1-sulphonic acid in that there is a strongly deactivating group in the 1-position. Further sulphonation of anthraquinone-1-sulphonic acid occurs solely in the other ring (Lauer, *J. pr. Chem.*, 1933, **137**, 176; Fierz-David, *loc. cit.*), and trisulphonic acids cannot be produced owing to the presence of the two deactivating groups (Lauer, *J. pr. Chem.*, 1932, **135**, 361). Since pyridine is sulphonated only in the 3-position under drastic conditions (cf. McElvaine and Goese, *J. Amer. Chem. Soc.*, 1943, **65**, 2333) 1-azanthraquinone was expected to sulphonate only in the benzene ring, and this was found to be the case, since only the 5-, 7-, and 8-sulphonic acids were isolated, and there was no evidence of disulphonation.

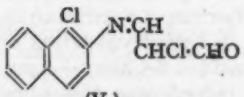
The three barium 1-azanthraquinonesulphonates were converted into the corresponding *chloro-1-azanthraquinones* by treatment with potassium chlorate and hydrochloric acid (D.R.-P. 597,833). The identity of these chloro-compounds was then established by synthesis or degradation.

3-Chloroquinoline has been prepared from indole by the action of alcoholic potash and chloroform (Ellinger, *Ber.*, 1906, **39**, 4388). Attempts to prepare 7-chloro-5 : 6-benzindole (II), which on similar treatment was expected to give 3 : 9-dichloro-1-azanthracene, from acetaldehyde 1-chloro-2-naphthylhydrazone by heating with zinc chloride failed, although

Schlieper (*Annalen*, 1886, **236**, 171) was able to convert acetaldehyde β-naphthylhydrazone into 4 : 5-benzindole. Attempts were then made to prepare (III) by Fischer's indole reaction on *ethyl pyruvate* 1-*chloro*-2-*naphthylhydrazone* with a view to obtain (II) by its decarboxylation. The ring closure, however, gave only the " angular " *isomer* (IV).



(IV.)



(V.)

Uhle and Jacobs (*J. Org. Chem.*, 1945, **10**, 76) described a new synthesis of 3-substituted quinolines. A substituted malonic dialdehyde is condensed with a primary amine and the product cyclised, angular cyclisation again being favoured. We attempted to prevent this by condensing 1-chloro-2-naphthylamine with chloromalonic dialdehyde to give the Schiff's *base* (V), which on cyclisation and oxidation gave a small yield of 3-*chloro*-1-*azanthraquinone*, m. p. 237—238°. This was different from any of the chloro-compounds obtained from the sulphonates.

5-Chloro-1-azanthraquinone was prepared from 1-chloro-5-amino-2-acetamidonaphthalene (Clemo and Driver, *J.*, 1945, 829) by a route analogous to that used by them for 5-bromo-1-azanthraquinone, and found to be identical with the chloro-1-azanthraquinone, m. p. 241—242°, obtained from one of the barium salts.

1-Chloro-2-acetamidonaphthalene on bromination gives 1-chloro-6-bromo-2-acetamidonaphthalene (Armstrong and Rossiter, *Chem. News*, 1891, **63**, 137) and hence it was expected that chlorination would give 1 : 6-dichloro-2-acetamidonaphthalene. The product obtained, however, was 1 : 4-*dichloro*-2-*acetamidonaphthalene* as proved by hydrolysis to the amine, and conversion of this into the known 1 : 4-dichloro- and 1 : 2 : 4-trichloro-naphthalenes. The *dichloro-amine* was also submitted to the Skraup reaction, and the product oxidised, 1-azanthraquinone being isolated. Similar selective halogenation has been observed in the case of 1-chloro-2-naphthol which on chlorination (Cleve, *Ber.*, 1888, **21**, 891) gives 1 : 4-dichloro-2-naphthol, whereas Armstrong and Rossiter (*Chem. News*, 1889, **59**, 225) found that on bromination 1-chloro-6-bromo-2-naphthol was formed.

1-Chloro-6-nitro-2-acetamidonaphthalene (Gerhardt and Hamilton, *J. Amer. Chem. Soc.*, 1944, **66**, 479) was reduced to the *amino*-compound, which was converted into 1 : 6-*dichloro*-2-*acetamidonaphthalene*. Hydrolysis, followed by the Skraup reaction and oxidation, gave 6-*chloro*-1-*azanthraquinone*, m. p. 265—266°, not identical with any of the chloroazanthraquinones formed from the sulphonic acids.

Attempts to prepare 7-chloro-2-naphthylamine as an intermediate for 7-chloro-1-azanthraquinone by the action of cuprous chloride in hydrochloric acid on the hydrochloride of the monodiazonium chloride of naphthylene-2 : 7-diamine (Kaufler and Karrer, *Ber.*, 1907, **40**, 3262) have failed.

1-Chloro-8-amino-2-acetamidonaphthalene (Clemo and Driver, *loc. cit.*) was converted into 1 : 8-*dichloro*-2-*naphthylamine* by the usual reactions. This was submitted to the Skraup reaction, and the product oxidised, but instead of the expected 8-chloro-1-azanthraquinone the only product which could be isolated was 6′-*chloro*-5 : 6-*benzoquinoline*.

Of the three chloro-1-azanthraquinones prepared from the sulphonic acids only one, the 5-isomer, had thus been orientated by synthesis. Attempts were made to orientate the other two isomers by oxidation. Johnson and Mathews (*J. Amer. Chem. Soc.*, 1944, **66**, 210) found that 2 : 4-dimethyl-1-azanthraquinone and (unexpectedly in view of the well-known resistance of the pyridine ring to oxidation) 1-azanthraquinone on oxidation with sulphuric acid and potassium permanganate both gave phthalic acid. It was therefore expected that 5-, 6-, 7- and 8-chloro-1-azanthraquinones on similar treatment would give 3-, 4-, 4- and 3-chlorophthalic acids, respectively. Synthesis having settled the orientations of the 5- and 6-chloro-isomers, it was therefore only necessary to apply the oxidation method to the two chloro-1-azanthraquinones of m. p.s 230—231° and 217—219°. These gave 4- and 3-chlorophthalic acids, respectively, thus proving the 7- and 8-positions (cf. table on p. 540).

A number of disubstituted 1-azanthraquinones have been prepared by nitration of some halogenated 1-azanthraquinones. 5-Chloro- and 8-chloro-1-azanthraquinone both gave a *mononitro*-derivative, presumably with the nitro-group in the *p*-position to the chlorine atom since Houben (*loc. cit.*, p. 288) states that α-chloroanthraquinones are nitrated in the *p*-position. 6-Bromo-1-azanthraquinone (E.P. 427,485) on nitration gave two *mononitro*-derivatives, but these disubstituted 1-azanthraquinone compounds have not been orientated.

Attempts to prepare hydroxy-1-azanthraquinones from the 1-azanthraquinonesulphonic acids by treatment with sodium carbonate solution (Iljinsky, *Ber.*, 1903, **36**, 4194), 20% sodium hydroxide solution (Simon, *Ber.*, 1881, **14**, 464), and calcium hydroxide (D.R.-P. 17,626) were unsuccessful. Schmidt (*Ber.*, 1904, **37**, 66), by using a solution of alkali in methanol, converted anthraquinonesulphonic acids into the corresponding hydroxy-compounds. This method when applied to barium 1-azanthraquinone-5-sulphonate gave a small yield of *5-hydroxy-1-azanthraquinone*. A better yield was obtained by using 5-chloro-1-azanthraquinone in place of the sulphonic acid. 8-Chloro-1-azanthraquinone was similarly converted into *8-hydroxy-1-azanthraquinone* which was also obtained by the same method from the nitro-1-azanthraquinone, m. p. 215—218° (Clemo and Driver, *loc. cit.*). This showed it to have the nitro-group in the 8-position, and on oxidation it gave 3-nitrophthalic anhydride. The 5-nitro-1-azanthraquinone which would have given a similar result on oxidation was synthesised by Gerhardt and Hamilton (*loc. cit.*).

6- and 7-Chloro-1-azanthraquinone on similar treatment with methanolic potassium hydroxide gave 6- and *7-methoxy-1-azanthraquinone*.

The formation of 5- and 8-hydroxy and of 6- and 7-methoxy-1-azanthraquinones from the chloro-1-azanthraquinones under identical conditions was also rather surprising, but it was believed that in all cases hydroxylation first took place, followed by subsequent methylation. This, however, took place only in the case of the 6- and 7-isomers, because of chelation in the 5- and 8-isomers between the hydroxyl and carbonyl groups (Sidgwick and Callow, *J.*, 1924, **125**, 527).

Experimental.

Sulphonation of 1-Azanthraquinone.—(1) Oleum (65%; 24 c.c.) was added to a finely divided mixture of 1-azanthraquinone (E.P. 420,485) (12 g.) and mercuric sulphate (0·3 g.) and heated at 95—98° for 6 hours. The solution was poured into ice-water (2 l.), and excess of barium carbonate added. The precipitate was filtered off and washed with boiling water (2 l.), and the combined filtrates evaporated to dryness, giving 20·2 g. of a mixture of barium salts. This was added to water (1350 c.c.) heated to 80°. The insoluble *barium 1-azanthraquinone-8-sulphonate* (6·7 g.) was collected [Found: Ba, 17·5; H_2O, 8·8. $(C_{13}H_6O_5NS)_2Ba,4H_2O$ requires Ba, 17·5; H_2O, 9·15%]. The *p-chlorobenzyl-ψ-thiouronium* derivative crystallised from dilute ethanol (1 : 1) in colourless plates, m. p. 265—266° (Found: C, 51·5; H, 3·1. $C_{21}H_{16}O_5N_2ClS_2$ requires C, 51·4; H, 3·3%).

The aqueous filtrate was concentrated to 750 c.c., and on standing a solid (6·3 g.) separated. This was collected and on recrystallisation from water gave *barium 1-azanthraquinone-5-sulphonate* (4·5 g.) in small, pale yellow needles [Found: Ba, 16·45; H_2O, 14·6. $(C_{13}H_6O_5NS)_2Ba,7H_2O$ requires Ba, 16·45; H_2O, 15·0%]. The *p-chlorobenzyl-ψ-thiouronate* crystallised from dilute ethanol in colourless needles, m. p. 227—228° (Found: C, 51·2; H, 3·2%). The aqueous filtrate on further concentration gave another 1·3 g. of the 5-sulphonate. The solution was concentrated further, and the solid (3·3 g.) collected. This crystallised from water to give *barium 1-azanthraquinone-7-sulphonate* (2·6 g.) as small, pale yellow needles [Found: Ba, 16·1; H_2O, 16·6. $(C_{13}H_6O_5NS)_2Ba,8H_2O$ requires Ba, 16·1; H_2O, 16·7%]. The *p-chlorobenzyl-ψ-thiouronate* crystallised from dilute alcohol in colourless plates, m. p. 215—216° (Found: C, 51·5; H, 3·4%).

The original solution on evaporation to dryness gave "BaV" (1·6 g.) as a pale red powder.

(2) Oleum (20%, 24 c.c.) was added to a mixture of 1-azanthraquinone (12 g.) and mercuric sulphate (0·3 g.) and heated at 150—155° for 3½ hours. The product was worked up as before, giving 20·3 g. of a mixture of barium salts. This was separated in the same manner as before to give 6·3, 2·7, and 3·8 g. of the 8-, 5-, and 7-sulphonates, respectively, and 2·6 g. of "BaV."

(3) 1-Azanthraquinone (4 g.) and oleum (20%; 16 c.c.) were heated together at 140—145° for 4 hours. The mixed barium salts (9·6 g.) were isolated as usual, and separated by fractional crystallisation from water, giving 2·6 and 0·95 g. of the 8- and the 7-sulphonate, respectively, and 5·2 g. of "BaV."

(4) 1-Azanthraquinone (3 g.) and sulphur trioxide (4 g.) were heated in a sealed tube to 170° during 2½ hours. The mixed barium salts (4·6 g.) gave on separation 1, 0·6, and 1·6 g. of the 8-, 5-, and 7-sulphonates, respectively, and 0·6 g. of "BaV."

Sulphonation of Decalin.—Nitrogen was passed over the surface of oleum (65%) and then bubbled through boiling decalin for 2 hours. The solid was filtered off, dissolved in water, and the solution filtered. Excess of barium carbonate was added to the filtrate, and the excess solid removed. The filtrate was evaporated, giving a barium salt (3 g.). This was dissolved in boiling water (20 c.c.), and a saturated solution of benzyl-ψ-thiouronium chloride (2 g.) in water added. The precipitate was collected and crystallised from dilute alcohol and then from dioxan, giving the *benzyl-ψ-thiouronate* of a decalin-sulphonic acid as colourless needles, m. p. 165—166° (Found: C, 56·0; H, 7·1; N, 7·3. $C_{18}H_{22}O_3N_2S_2$ requires C, 56·2; H, 7·3; N, 7·3%).

Orientation of the Barium 1-Azanthraquinonesulphonates by Conversion into Chloro-1-azanthraquinones.—*5-Chloro-1-azanthraquinone.* To a hot solution of barium 1-azanthraquinone-5-sulphonate (0·4 g.) in water (20 c.c.) and concentrated hydrochloric acid (8 c.c.) was added, during 2 hours, a hot solution of potassium chlorate (2 g.) in water (40 c.c.). After refluxing for a further 2 hours, the solution was cooled and basified. The solid was collected and extracted with chloroform. The solvent was distilled off and the residue crystallised from acetic acid, giving yellow needles of *5-chloro-1-azanthraquinone* (0·1 g.), m. p. 240—241°, not depressed by admixture with an authentic specimen (see later).

7-Chloro-1-azanthraquinone, similarly prepared from the 7-sulphonate (0·5 g.), crystallised from acetic acid in yellow needles (0·08 g.; m. p. 230—231°) (Found: C, 64·0; H, 2·3. $C_{13}H_6O_2NCl$ requires C,

64·1; H, 2·5%). Oxidation by the method of Johnson and Mathews (*loc. cit.*) gave 4-chlorophthalic anhydride, and since 6-chloro-1-azanthraquinone has been synthesised (see later) this must be the 7-isomer.

8-Chloro-1-azanthraquinone, similarly prepared from the 8-sulphonate (1 g.), crystallised in pale yellow needles (0·1 g.; m. p. 217—219°) from acetic acid (Found: C, 64·2; H, 2·6%). Oxidation by Johnson and Mathews's method gave 3-chlorophthalic anhydride, thus providing the identity of 8-chloro-1-azanthraquinone.

3-Chloro-1-azanthraquinone.—(a) *1-Chloro-2-naphthylhydrazine.* A solution of diazotised 1-chloro-2-naphthylamine (20 g.) (Cleve, *Ber.*, 1887, **20**, 1990) was run into one of stannous chloride (50 g.) in hydrochloric acid (100 c.c.). After 1 hour the hydrazine hydrochloride was collected and basified. The precipitated *1-chloro-2-naphthylhydrazine* was filtered off, washed, dried, and crystallised from dilute alcohol, forming glistening white leaflets which rapidly darkened (15 g.; m. p. 110—111°) (Found: C, 62·7; H, 4·4. $C_{10}H_9N_2Cl$ requires C, 62·5; H, 4·7%).

Pyruvic acid 1-chloro-2-naphthylhydrazone. To a solution of the hydrazine (15 g.) in acetic acid (60 c.c.) and water (35 c.c.) pyruvic acid (9 g.) and water (42 c.c.) were added. The precipitated *hydrazone* (18·5 g.) was collected, and crystallised from dilute alcohol in pale yellow needles, m. p. 188 189° (decomp.) (Found: C, 59·5; H, 4·3. $C_{13}H_{11}O_2N_2Cl$ requires C, 59·4; H, 4·2%).

Ethyl pyruvate 1-chloro-2-naphthylhydrazone was prepared by refluxing the acid hydrazone (15 g.) with absolute alcohol (150 c.c.) and concentrated sulphuric acid (15 c.c.) for 2 hours. The solution was poured into water, and the solid collected. Crystallisation from alcohol gave pale yellow needles (15 g.; m. p. 92—93°) (Found: C, 60·3; H, 5·1. $C_{15}H_{15}O_2N_2Cl$ requires C, 60·2; H, 5·4%).

2-Carbethoxy-4:5-benzindole. The above hydrazone (2 g.) was heated with glacial acetic acid (10 c.c.) and concentrated sulphuric acid (0·7 c.c.) on a water-bath for 1 hour. Addition of water precipitated a solid, which was collected and crystallised successively from benzene–light petroleum (b. p. 60—80°) and methanol to give *2-carbethoxy-4:5-benzindole* (2 g.), m. p. 161—162° (Found: C, 75·3; H, 5·6. $C_{15}H_{13}O_2N$ requires C, 75·3; H, 5·4%).

(b) *Chloromalonic dialdehyde.* 1:2:3:3-Tetrachloropropyl-1-ene (Heilbron, Heslop, and Irving, *J.*, 1936, 781) (15 g.) and concentrated sulphuric acid (50 c.c.) were stirred together for 6 hours at 45°. Ice (200 g.) was added, and the solution extracted twice with chloroform (50 c.c.). The chloromalonic dialdehyde was extracted with ether, and the ether distilled off, leaving the aldehyde (6 g.), m. p. 142—144° (lit. m. p. 144—145°).

2'-Chloro-2'-formylethylidene-1-chloro-2-naphthylamine. Chloromalonic dialdehyde (2 g.), dissolved in N/5-sodium hydroxide solution (500 c.c.), was added with stirring to a hot suspension of 1-chloro-2-naphthylamine (3 g.) in hydrochloric acid (100 c.c., 2%). When cold, the solid was collected and crystallised from alcohol to give nearly colourless needles (4·3 g.; m. p. 227—228°) (Found: C, 58·7; H, 3·3. $C_{13}H_9ONCl_2$ requires C, 58·6; H, 3·4%).

(c) *3-Chloro-1-azanthraquinone.* The above Schiff's *base* (3·5 g.) and powdered fused zinc chloride (3·5 g.) were well mixed and heated at 290—300° until molten. When cold, the solid was powdered and extracted with hot hydrochloric acid (1 : 1). The acid extract was basified, and the oil separated. It was dissolved in acetic acid (15 c.c.), heated on the water-bath with chromic anhydride (2 g.) for 1 hour, and poured into saturated brine (25 c.c.). The solution was extracted with benzene, the benzene extracts washed with sodium hydroxide solution and water, and finally dried. Removal of the benzene gave *3-chloro-1-azanthraquinone* which crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow needles (50 mg.; m. p. 237—238°) (Found: C, 64·2; H, 2·6; N, 5·8. $C_{13}H_6O_2NCl$ requires C, 64·1; H, 2·5; N, 5·75%).

5-Chloro-1-azanthraquinone.—(a) *1:5-Dichloro-2-acetamidonaphthalene.* 1-Chloro-5-amino-2-acetamidonaphthalene (Clemo and Driver, *loc. cit.*) (10·7 g.) in glacial acetic acid (65 c.c.) was added below 25° to a stirred solution of sodium nitrite (3·7 g.) in concentrated sulphuric acid (37 c.c.). The diazo-solution was run into a solution of cuprous chloride (40 g.) in concentrated hydrochloric acid (250 c.c.). After nitrogen evolution had ceased, water (500 c.c.) was added, and the solid collected. It crystallised from alcohol in white needles (8 g.; m. p. 180—181°) (Found: C, 56·5; H, 3·5. $C_{12}H_9ONCl_2$ requires C, 56·7; H, 3·5%).

(b) *1:5-Dichloro-2-naphthylamine.* The *acetyl* compound (7·0 g.) was refluxed with alcohol (70 c.c.) and concentrated hydrochloric acid (35 c.c.) for 1 hour, water (300 c.c.) added, and the solution basified. The *amine* was collected, and crystallised from alcohol giving colourless needles (5 g.; m. p. 124—125°) (Found: C, 56·8; H, 3·4. $C_{10}H_7NCl_2$ requires C, 56·6; H, 3·3%).

(c) *5-Chloro-1-azanthraquinone.* The amine (5 g.) and sulphuric acid (50 c.c.; 66%) were heated under reflux, and glycerol (5 g.) and sodium *m*-nitrobenzenesulphonate (7·5 g.) added during ½ hour, refluxing being continued for a further 5 hours. Water was added, the solution basified, and the black solid collected, washed, dried, and extracted with acetone. Removal of the acetone left a yellow solid which was oxidised by dissolving it in acetic acid (50 c.c.), adding chromic anhydride (6 g.), and heating the mixture on a water-bath for 1 hour. Water was added, and the solid collected, washed, dried, and extracted with boiling chlorobenzene. Removal of the solvent left yellow needles (1·5 g.; m. p. 240—241°, raised to 243—244° by crystallisation from acetic acid) (Found: C, 63·9; H, 2·8%).

6-Chloro-1-azanthraquinone.—(a) *Chlorination of 1-chloro-2-acetamidonaphthalene.* Chlorine, prepared from potassium permanganate (20 g.) and hydrochloric acid, was bubbled slowly during 3 hours through a boiling solution of 1-chloro-2-acetamidonaphthalene (20 g.) in glacial acetic acid (200 c.c.). On cooling, *1:4-dichloro-2-acetamidonaphthalene* crystallised. Recrystallisation from alcohol gave white leaflets (6·3 g.; m. p. 212—213°) (Found: C, 56·5; H, 3·4; Cl, 27·8. $C_{12}H_9ONCl_2$ requires C, 56·7; H, 3·5; Cl, 28·0%). Unchanged material (12·5 g.) was recovered from the acetic acid mother-liquor.

1:4-Dichloro-2-naphthylamine, prepared by hydrolysis of the acetyl derivative with hydrochloric acid and alcohol, crystallised from methanol in white needles, m. p. 92—93° (Found: C, 56·8; H, 3·3; Cl, 33·3. $C_{10}H_7NCl_2$ requires C, 56·6; H, 3·3; Cl, 33·5%). That chlorination had occurred in the 4-position was established by converting the amine into the known 1:4-dichloro- and 1:2:4-trichloro-

naphthalenes. A Skraup reaction on the amine, using the same method as for the 5-isomer, gave 1-azanthraquinone after oxidation.

(b) 1-*Chloro*-6-*amino*-2-*acetamidonaphthalene*. Iron filings (40 g.) were etched by vigorous stirring for ½ hour with alcohol (66 c.c.) and concentrated hydrochloric acid (14 c.c.) and refluxing for 15 mins. The alcohol was decanted, and the etched iron washed twice with water. 1-Chloro-6-nitro-2-acetamidonaphthalene (Gerhardt and Hamilton, *loc. cit.*) (8 g.) in alcohol (400 c.c.) was added, the mixture refluxed with stirring for 5 hours, filtered, and the alcohol evaporated. The residue crystallised from dilute acetic acid in white needles (6 g.; m. p. 159—160°) (Found: C, 61·6; H, 4·5. $C_{12}H_{11}ON_2Cl$ requires C, 61·4; H, 4·7%).

1 : 6-*Dichloro*-2-*acetamidonaphthalene* was prepared from the above amine (6·3 g.) in the same manner as the 1 : 5-isomer. It crystallised from alcohol in white needles (5·3 g.; m. p. 219—220°) (Found: C, 56·9; H, 3·7%).

1 : 6-*Dichloro*-2-*naphthylamine* was prepared by hydrolysis of the acetyl compound and crystallised from alcohol, m. p. 100—101° (Found: C, 56·6; H, 3·5%).

6-*Chloro*-1-*azanthraquinone* was prepared from 1 : 6-dichloro-2-naphthylamine (5 g.) in the same manner as the 5-isomer, and crystallised as pale yellow needles (1 g.; m. p. 265—266°) from acetic acid (Found: C, 64·3; H, 2·6%).

Attempted Synthesis of 8-*Chloro*-1-*azanthraquinone*.—1 : 8-*Dichloro*-2-*acetamidonaphthalene* was prepared from 1-chloro-8-amino-2-acetamidonaphthalene (Clemo and Driver, *loc. cit.*) (8·5 g.) in the same manner as the 1 : 5- and the 1 : 6-isomer. Crystallisation from alcohol gave white needles (4·9 g., m. p. 146—147°) (Found: C, 56·6; H, 3·7%).

1 : 8-*Dichloro*-2-*naphthylamine*, obtained by hydrolysis of the acetyl compound, crystallised from methanol in colourless needles, m. p. 71—72° (Found: C, 56·7; H, 3·5%). This amine (2·5 g.) was submitted to the Skraup reaction under the above conditions but gave only 6′-*chloro*-5 : 6-*benzoquinoline* (0·5 g.), crystallising from light petroleum (b. p. 60—80°) in colourless needles, m. p. 89—90° (Found: C, 73·0; H, 3·6; N, 6·4. $C_{13}H_8NCl$ requires C, 72·9; H, 3·7; N, 6·5%).

Nitration of Some Halogeno-1-*azanthraquinones*.—6-Bromoazanthraquinone (E.P. 427,485) (3 g.) was heated for 1 hour on the water-bath with a mixture of concentrated sulphuric acid (60 c.c.) and concentrated nitric acid (6 c.c.), the solution poured on ice and basified, and the solid collected. Fractional crystallisation from acetic acid gave 6-*bromo*-x-*nitro*-1-*azanthraquinone* (2 g.) as yellow needles, m. p. 292—293° (Found: C, 47·0; H, 1·6. $C_{13}H_5O_4N_2Br$ requires C, 46·8; H, 1·5%), and 6-*bromo*-y-*nitro*-1-*azanthraquinone* (0·3 g.) as yellow needles, m. p. 255—256° (Found: C, 46·5; H, 1·75%).

5-Chloro-1-azanthraquinone (0·2 g.) when nitrated as above gave 5-*chloro*-8(?)-*nitro*-1-*azanthraquinone* (0·15 g.) as bright yellow needles (from dilute acetic acid), m. p. 257—258° (Found: C, 54·0; H, 1·9. $C_{13}H_5O_4N_2Cl$ requires C, 54·0; H, 1·7%). 6-Chloro-1-azanthraquinone (0·2 g.) on similar treatment gave 6-*chloro*-x-*nitro*-1-*azanthraquinone* (0·1 g.) as pale yellow needles, m. p. 283—284°, from dilute acetic acid (Found: C, 54·2; H, 2·0%). 8-Chloro-1-azanthraquinone (0·1 g.) on nitration gave 8-*chloro*-5(?)-*nitro*-1-*azanthraquinone* (0·08 g.) as orange needles, m. p. 222—223°, from dilute acetic acid (Found: C, 54·1; H, 1·8%).

All the above nitro-compounds slowly darkened on exposure to light.

5-*Hydroxy*-1-*azanthraquinone*.—(*a*) 5-Chloro-1-azanthraquinone (0·3 g.) and a solution of potassium hydroxide in methanol (15 c.c.; 2%) were heated together in a sealed tube for 18 hours at 100°. Water was added, the methanol removed, the residual solution just acidified with acetic acid, and the *hydroxyazanthraquinone* extracted with chloroform. Removal of the solvent left a yellow solid (0·25 g.) which, after crystallisation from water and sublimation at 1 mm., was obtained as bright yellow needles, m. p. 214—215° (Found: C, 69·1; H, 3·2. $C_{13}H_7O_3N$ requires C, 69·3; H, 3·1%).

(*b*) Barium 1-azanthraquinone-5-sulphonate (0·3 g.) on similar treatment gave 5-hydroxy-1-azanthraquinone (30 mg.).

8-*Hydroxy*-1-*azanthraquinone*.—(*a*) 8-Chloro-1-azanthraquinone (0·3 g.) when similarly treated gave 8-*hydroxy*-1-*azanthraquinone* (0·23 g.) which, after crystallisation from water and sublimation at 1 mm., was obtained as bright yellow needles, m. p. 199—200° (Found: C, 69·5; H, 3·3%).

(*b*) The nitro-azanthraquinone (m. p. 215—218°) (Clemo and Driver, *loc. cit.*) (0·3 g.) when similarly treated gave 8-hydroxy-1-azanthraquinone (0·2 g.), m. p. and mixed m. p. 197—199°. The nitro-group is therefore in the 8-position, and this was confirmed by oxidation with acid permanganate (Johnson and Mathews, *loc. cit.*), 3-nitrophthalic anhydride being obtained.

6-*Methoxy*-1-*azanthraquinone*.—6-Bromo-1-azanthraquinone (1 g.) and methanolic potassium hydroxide solution (50 c.c.; 2%) were heated for 18 hours at 100° in a sealed tube. The methanol was removed, water added, and the solid (0·7 g.) collected. This was again heated with the potassium hydroxide solution (35 c.c.) as before, and the solid isolated and crystallised from acetic acid, to give 6-*methoxy*-1-*azanthraquinone* (0·5 g.) as yellow needles, m. p. 259—261° (Found: C, 70·3; H, 3·8. $C_{14}H_9O_3N$ requires C, 70·3; H, 3·8%).

7-*Methoxy*-1-*azanthraquinone*, similarly prepared from 7-chloro-1-azanthraquinone (0·2 g.), crystallised from acetic acid in pale yellow needles (0·1 g.), m. p. 205—207° (Found: C, 70·1; H, 3·6%).

Our thanks are due to Imperial Chemical Industries (Dyestuffs) Ltd. for the gift of materials and a research grant to one of us (N. L.).

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NEWCASTLE-UPON-TYNE.

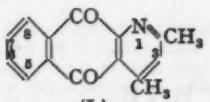
[*Received, July 23rd,* 1946.]

104. *The Chemistry of 1-Azanthraquinone. Part III. Chloro-derivatives of 2 : 4-Dimethyl-1-azanthraquinone.*

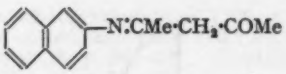
By G. R. Clemo and N. Legg.

An improved synthesis of 2 : 4-dimethyl-1-azanthraquinone (I) is described. Attempts to sulphonate (I) to give monosulphonic acids failed. 5-, 6-, and 8-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinones* have been synthesised from the hitherto unknown 5-, 6-, and 8-*chloro*-2-*naphthylamines*. Attempts to synthesise 3- and 7-chloro-2 : 4-dimethyl-1-azanthraquinones have failed.

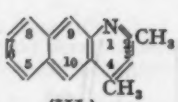
2 : 4-Dimethyl-1-azanthraquinone (I) was first synthesised by Johnson and Mathews (*J. Amer. Chem. Soc.*, 1944, **66**, 210) by condensing β-naphthylamine with acetylacetone to give 4-(2′-naphthylimino)pentan-2-one (II) and then cyclising this in sulphuric acid to 2 : 4-dimethyl-1-azanthracene (III) which on oxidation gave (I). It has been found possible to improve the original synthesis so that larger quantities of (I) can be readily prepared.



(I.)



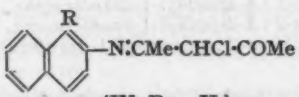
(II.)



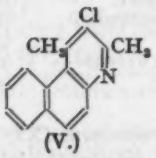
(III.)

Attempts have been made to sulphonate (I) on the same lines as those used for 1-azanthraquinone (Part II, preceding paper). Concentrated sulphuric acid at 100° and 150°, with and without a mercury catalyst, failed to react, as did also chlorosulphonic acid at 200°. The use of sulphur trioxide at 170°, and 20% oleum, with and without a mercury catalyst, at 100° and 150° caused evolution of sulphur dioxide and formation of oxidation products which were probably polyhydroxysulphonic acids, since they closely resembled polyhydroxyanthraquinonesulphonic acids in their properties. The use of sulphur trioxide (1 or 2 mols.) in chlorosulphonic acid at 100° and 150° also gave rise to oxidation products, although some of the quinone (I) was recovered.

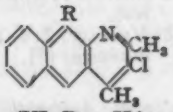
Synthesis of Chloro-2 : 4-*dimethyl*-1-*azanthraquinones.*—3-Chloroacetylacetone (Combes, *Compt. rend.*, 1890, **111**, 273) was heated with β-naphthylamine at 100°, but instead of the expected 3-*chloro*-4-(2′-*naphthylimino*)*pentan*-2-*one* (IV), acet-β-naphthalide was produced quantitatively. β-Naphthylamine reacted with 3-chloroacetylacetone in neutral aqueous solution to give (IV), which on cyclisation in 90% sulphuric acid gave 3-*chloro*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (V), instead of 3-chloro-2 : 4-dimethyl-1-azanthracene (VI). Proof that angular cyclisation had occurred was obtained from a study of the absorption spectra (Fig. 1) (cf. Johnson and Mathews, *loc. cit.*).



(IV, R = H.)
(VII, R = Cl.)

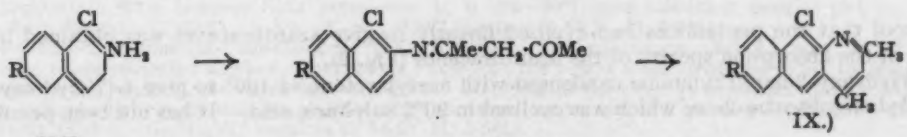


(V.)



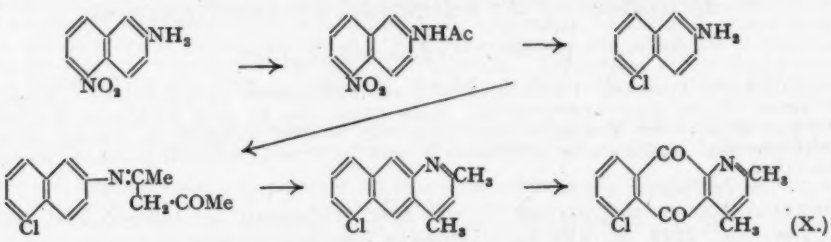
(VI, R = H.)
(VIII, R = Cl.)

1-Chloro-2-naphthylamine condensed with 3-chloroacetylacetone at 100° to give 3-*chloro*-4-(1′-*chloro*-2′-*naphthylimino*)*pentan*-2-*one* (VII), which on cyclisation gave 3 : 9-*dichloro*-2 : 4-*dimethyl*-1-*azanthracene* (VIII). Attempts to oxidise (VIII) to 3-chloro-2 : 4-dimethyl-1-azanthraquinone by potassium dichromate or chromic anhydride in acetic acid, however, failed, the azanthracene being recovered quantitatively. It was also found that 9-*chloro*- (IX, R = H) and 9-*chloro*-6-*bromo*-2 : 4-*dimethyl*-1-*azanthracene* (IX, R = Br), prepared as shown, could not be oxidised to the corresponding quinones. These results are in striking contrast to the easy oxidation of 9-chloro-azanthracenes to the corresponding quinones (Part II, *loc. cit.*).



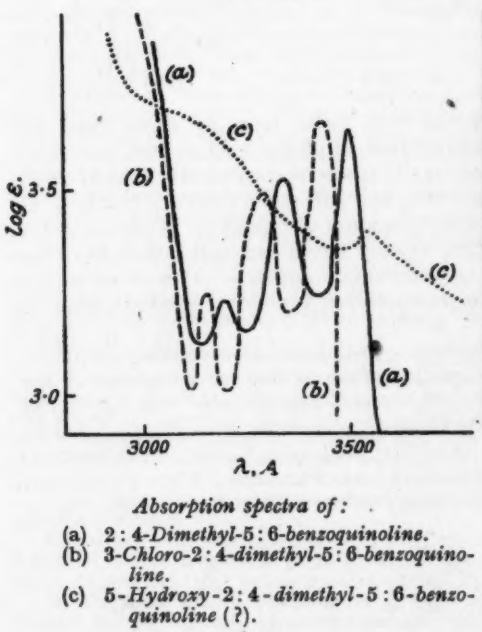
IX.)

5-Chloro-2 : 4-dimethyl-1-azanthraquinone (X) has been synthesised from 5-nitro-2-naphthylamine (Cohen *et al.*, *J.*, 1934, 656) by the following route :



8-Chloro-2 : 4-dimethyl-1-azanthraquinone was similarly prepared from 8-nitro-2-naphthylamine (Saunders and Hamilton, *J. Amer. Chem. Soc.*, 1932, **54**, 638).

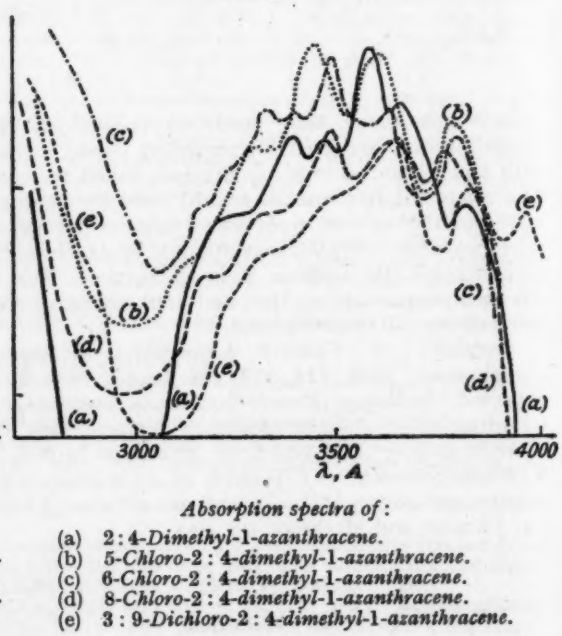
FIG. 1.



Absorption spectra of :

(a) 2 : 4-*Dimethyl*-5 : 6-*benzoquinoline.*
(b) 3-*Chloro*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline.*
(c) 5-*Hydroxy*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (?).

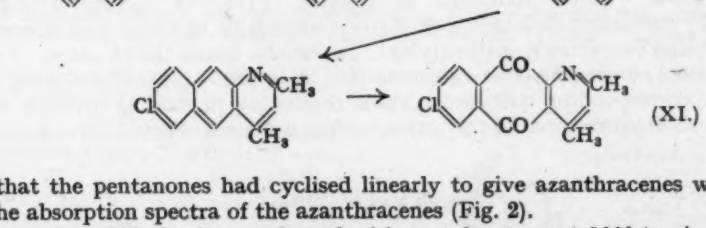
FIG. 2.



Absorption spectra of :

(a) 2 : 4-*Dimethyl*-1-*azanthracene.*
(b) 5-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene.*
(c) 6-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene.*
(d) 8-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene.*
(e) 3 : 9-*Dichloro*-2 : 4-*dimethyl*-1-*azanthracene.*

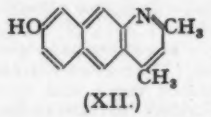
6-Chloro-2 : 4-dimethyl-1-azanthraquinone (XI) has been synthesised from 6-nitro-2-naphthylamine (Saunders and Hamilton, *loc. cit.*) by the following route :



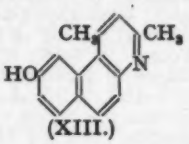
Proof that the pentanones had cyclised linearly to give azanthracenes was obtained by a study of the absorption spectra of the azanthracenes (Fig. 2).

7-Hydroxy-2-naphthylamine condensed with acetylacetone at 100° to give *4-(7'-hydroxy-2'-naphthylimino)pentan-2-one* which was cyclised in 90% sulphuric acid. It has not been possible,

however, to decide whether the *product* has structure (XII) or (XIII) since the absorption spectrum (Fig. 1) does not resemble that of either azanthracenes or 5 : 6-benzoquinolines.



(XII.)



(XIII.)

Attempts to replace the hydroxyl group by chlorine by treatment with phosphorus pentachloride, with and without benzene as a solvent, phosphorus oxychloride in tetrachloroethane, a mixture of phosphorus oxychloride and pentachloride, and refluxing the sodium salt with phosphorus oxychloride failed. Attempts to replace the hydroxyl by the amino-group, which could then be converted into the chloro-compound, by treatment with concentrated aqueous ammonia at 240° and a zinc chloride–ammonia complex at 260° also failed.

Experimental.

4-(2'-Naphthylimino)pentan-2-one.—β-Naphthylamine (200 g.) and acetylacetone (240 c.c.) were heated on a water-bath for 4 hours, cooled, and ether (10 c.c.) added. The solid obtained was then pressed on a porous plate; yield 300 g., m. p. 96—99°. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave pale yellow needles, m. p. 98—99°.

2 : 4-Dimethyl-1-azanthracene.—The pentanone (250 g.) was powdered and added to sulphuric acid (850 c.c. of 90%) below 60°, and the yellow solution heated on a water-bath for ½ hour, and poured on ice (3000 g.). The sulphate was collected, stirred into water (3 l.), excess of ammonia added, and the liberated base taken up in benzene. The benzene extract was dried, the solvent removed, and the residue distilled at 1 mm. and then crystallised from benzene, giving pale yellow needles (175 g.), m. p. 92—93°. [Our thanks are due to Dr. MacDonald, Research Department, I.C.I. (Dyestuffs) Ltd., for these experimental details.]

2 : 4-Dimethyl-1-azanthraquinone.—The azanthracene (49 g.), glacial acetic acid (1350 c.c.), water (90 c.c.), and potassium dichromate (70·5 g.) were refluxed for 3 hours, and the solution concentrated in vacuum by removal of 1100 c.c. of solvent. The residue was dissolved in water and basified with sodium hydroxide solution, and the solid collected, washed with water, dried, and extracted with benzene (Soxhlet). The benzene was removed, and the residue crystallised from benzene–light petroleum (b. p. 100—120°) to give 2 : 4-dimethyl-1-azanthraquinone as yellow needles (25 g.), m. p. 214—216° (Johnson and Mathews, *loc. cit.*, give m. p. 215—216°).

Attempted Synthesis of 3-Chloro-2 : 4-dimethyl-1-azanthraquinone.—(a) *3-Chloro-4-(2'-naphthylimino)pentan-2-one.* (1) β-Naphthylamine (0·7 g.) and 3-chloroacetylacetone (0·86 g.) were heated on a water-bath for 3 hours, and the solid collected and crystallised from benzene–light petroleum (b. p. 60—80°) to give colourless plates (0·7 g.) of acet-β-naphthalide, m. p. and mixed m. p. 132—134°. (2) β-Naphthylamine (2 g.), concentrated hydrochloric acid (4 c.c.), and water (80 c.c.) were warmed to 60°, and a suspension of 3-chloroacetylacetone (2 g.) in N/5-sodium hydroxide solution (74 c.c.) added with stirring. After 3 hours the solid was collected, washed with water and dried. The *3-chloro-4-(2'-naphthylimino)pentan-2-one* crystallised from light petroleum (b. p. 60—80°) in colourless needles (2·8 g.), m. p. 96—97° (Found : C, 69·5; H, 5·4. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

(b) *3-Chloro-2 : 4-dimethyl-5 : 6-benzoquinoline* (V). The above compound (2·8 g.) and sulphuric acid (14 c.c. of 90%) were heated on a water-bath for ½ hour, the solution poured into water, basified, and the solid collected and crystallised from light petroleum (b. p. 60—80°) to give colourless needles (1·8 g.), m. p. 143—144° (Found : C, 74·3; H, 4·8. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0%). Ultra-violet absorption spectrum (0·000249M-solution in hexane) : Maxima at 3200 A. (ε 1660), 3350 A. (ε 3390), and 3510 A. (ε 4470).

(c) *3-Chloro-4-(1'-chloro-2'-naphthylimino)pentan-2-one.* 1-Chloro-2-naphthylamine (8·4 g.) and 3-chloroacetylacetone (6·3 g.) were heated on a water-bath for 2 hours, and the water and excess of ketone distilled off under reduced pressure. The black residue was stirred with benzene (10 c.c.), and the yellow solid which was filtered off (4·5 g.) was crystallised from benzene–light petroleum (b. p. 60—80°), affording colourless needles, m. p. 137—138° (Found : C, 61·6; H, 4·5; N, 5·0. $C_{15}H_{13}ONCl_2$ requires C, 61·2; H, 4·3; N, 4·8%).

(d) *3 : 9-Dichloro-2 : 4-dimethyl-1-azanthracene* (VIII). The pentanone (3·5 g.) and sulphuric acid (18 c.c. of 90%) were heated on a water-bath for ½ hour, the solution poured on ice and basified, and the solid collected. Crystallisation from benzene gave colourless needles (3 g., m. p. 224—225°) (Found : C, 65·1; H, 4·1; N, 5·1. $C_{15}H_{11}NCl_2$ requires C, 65·2; H, 4·0; N, 5·0%). Ultra-violet absorption spectrum (0·000261M-solution in absolute alcohol) : Maxima at 3350 A. (inflexion) (ε2290), 3500A. (ε 3160), 3650 A. (ε 4470), 3770 A. (ε 3800), and 3970 A. (ε 2880).

4-(1'-Chloro-2'-naphthylimino)pentan-2-one. 1-Chloro-2-naphthylamine (5 g.) and acetylacetone (4 c.c.) were heated on a water-bath for 4 hours, cooled, and ether (1 c.c.) added; the oil then solidified. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave colourless needles (3·1 g., m. p. 87—88°) (Found : C, 69·5; H, 5·4. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

9-Chloro-2 : 4-dimethyl-1-azanthracene (IX, R = H). The pentanone (2·5 g.) was added, with stirring, to concentrated sulphuric acid (10 c.c.) at 0—2°, the yellow solution heated to 60° for 2 minutes, poured on ice, basified, and extracted with ether. Removal of the ether gave a solid which crystallised from benzene–light petroleum (b. p. 100—120°) in colourless needles (1·2 g., m. p. 166—167°) (Found : C, 74·6; H, 5·1. $C_{15}H_{12}NCl$ requires C, 74·5; H, 5·0%).

4-(1′-*Chloro*-6′-*bromo*-2′-*naphthylimino*)*pentan*-2-*one*, from 1-chloro-6-bromo-2-naphthylamine (5 g.) and acetylacetone (4 c.c.), crystallised from light petroleum (b. p. 100—120°) in white needles (3·0 g., m. p. 133—134°) (Found: C, 53·0; H, 3·8. $C_{15}H_{13}ONClBr$ requires C, 53·2; H, 3·8%).

9-*Chloro*-6-*bromo*-2 : 4-*dimethyl*-1-*azanthracene* (IX, R = Br) was prepared by cyclising the pentanone (3 g.) with sulphuric acid (15 c.c. of 90%). It crystallised from ethanol as colourless needles, (2·1 g., m. p. 166—168°) (Found: C, 56·0; H, 3·4. $C_{15}H_{11}NClBr$ requires C, 56·1; H, 3·4%).

5-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone* (X).—(a) 5-*Amino*-2-*acetamidonaphthalene*. Iron filings (100 g.), alcohol (170 c.c.), and concentrated hydrochloric acid (37 c.c.) were stirred for ½ hour and refluxed for 10 minutes, the liquid decanted, and the iron washed twice with water. A solution of 5-nitro-2-acetnaphthalide (15·2 g.) in alcohol (400 c.c.) was added to the etched iron and stirred under reflux for 4 hours. The mixture was filtered, the residue washed with boiling alcohol (100 c.c.), and the combined filtrates concentrated, 5-amino-2-acetnaphthalide (11·4 g., m. p. 132—134°) being obtained. Crystallisation from dilute ethanol gave colourless needles, m. p. 136—137° (Found: C, 72·2; H, 5·9. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%).

(b) 5-*Chloro*-2-*acetnaphthalide*. The amino-compound (10 g.) in glacial acetic acid (100 c.c.) was added to a solution of sodium nitrite (5·0 g.) in concentrated sulphuric acid (50 c.c.), the temperature being kept below 20°. After ½ hour the solution was added to cuprous chloride (30 g.) in concentrated hydrochloric acid (200 c.c.). After 20 hours, water (700 c.c.) was added, and the solid collected and crystallised from ethanol to give light brown needles (8·5 g., m. p. 147—148°) (Found: C, 65·6; H, 4·6. $C_{12}H_{10}ONCl$ requires C, 65·5; H, 4·55%).

(c) 5-*Chloro*-2-*naphthylamine*. The acetyl derivative (8 g.), alcohol (100 c.c.), and concentrated hydrochloric acid (50 c.c.) were refluxed for 1 hour, the solution poured into water and basified, the oil extracted with benzene, and the benzene extract dried. The benzene was removed, and the residue distilled at 1 mm. to give a pale yellow oil (6 g.) which rapidly solidified. Crystallisation from light petroleum (b. p. 40—60°) gave colourless needles, m. p. 35—36° (Found: C, 67·9; H, 4·3. $C_{10}H_8NCl$ required C, 67·6; H, 4·5%).

(d) 4-(5′-*Chloro*-2′-*naphthylimino*)*pentan*-2-*one* was prepared from 5-chloro-2-naphthylamine (3·5 g.) and acetylacetone (4·5 c.c.). It crystallised from light petroleum (b. p. 60—80°) in pale yellow needles (3·5 g., m. p. 68—69°) (Found: C, 69·5; H, 5·25. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

(e) 5-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene*. The pentanone (3·4 g.) was cyclised in sulphuric acid (17 c.c. of 90%). The *azanthracene* crystallised from light petroleum (b. p. 60—80°) in white needles (2·6 g., m. p. 145—146°) (Found: C, 74·5; H, 4·85. $C_{15}H_{12}NCl$ requires C, 74·4; H, 5·0%). Ultra-violet absorption spectrum (0·000318M-solution in hexane): maxima at 3150 A. (inflexion) (ε 2240), 3300 A. (ε 4070), 3340 A. (ε 4070), 3450 A. (ε 7240), 3610 A. (ε 7080), and 3800 A. (ε 4786).

(f) 5-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*. Chromic anhydride (0·5 g.) was added to a solution of the azanthracene (0·5 g.) in glacial acetic acid (15 c.c.), and the mixture heated for 1½ hours on a water-bath, poured into saturated brine (25 c.c.), and extracted with benzene. The benzene extracts were washed with sodium hydroxide solution and water and dried. The benzene was removed, and the residue crystallised from benzene–light petroleum (b. p. 60—80°) to give bright yellow plates (25 mg., m. p. 210—211°) (Found: C, 66·4; H, 3·7. $C_{15}H_{10}O_2NCl$ requires C, 66·2; H, 3·7%).

Synthesis of 6-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*.—(a) 6-*Chloro*-2-*nitronaphthalene*. A suspension of 6-nitro-2-naphthylamine (20 g.) in glacial acetic acid (200 c.c.) was added, with stirring, to a solution of sodium nitrite (10 g.) in concentrated sulphuric acid (100 c.c.), the temperature being kept below 20°. After ½ hour the diazo-solution was added to cuprous chloride (50 g.) dissolved in concentrated hydrochloric acid (400 c.c.). After 25 hours water (1000 c.c.) was added, and the solid collected and crystallised from ethanol to give pale yellow needles (19·1 g., m. p. 181—182°) (Found: C, 57·8; H, 2·9. $C_{10}H_6O_2NCl$ requires C, 57·8; H, 2·9%).

(b) 6-*Chloro*-2-*naphthylamine*. The nitro-compound (18 g.) in alcohol (500 c.c.) was reduced by etched iron (from iron filings, 120 g.). After removal of the iron residues, the alcohol was distilled from a water-bath, and the residue crystallised twice from light petroleum (b. p. 60—80°) to give colourless needle (14·5 g., m. p. 120—121°) (Found: C, 67·8; H, 4·3. $C_{10}H_8NCl$ requires C, 67·6; H, 4·5%). The *acetyl* derivative, from the *amine* and acetic anhydride, crystallised from ethanol in white needles, m. p. 184—185° (Found: C, 65·3; H, 4·6. $C_{12}H_{10}ONCl$ required C, 65·5; H, 4·55%).

(c) 4-(6′-*Chloro*-2′-*naphthylimino*)*pentan*-2-*one* was prepared in the same manner as the 5-isomer from 6-chloro-2-naphthylamine (8 g.). It crystallised from light petroleum (b. p. 60—80°) in colourless needles (10·5 g., m. p. 110—111°) (Found: C, 69·6; H, 5·3. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

(d) 6-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene*. The pentanone (9 g.) was cyclised as before. Crystallisation from light petroleum (b. p. 60—80°) gave colourless needles (7·2 g., m. p. 130—131°) (Found: C, 74·6; H, 4·95. $C_{15}H_{12}NCl$ requires C, 74·4; H, 5·0%). Ultra-violet absorption spectrum (0·000248M-solution in hexane): Maxima at 3170 A. (inflexion) (ε 2880), 3320 A. (ε 5010), 3400 A. (ε 5010), 3490 A. (ε 6760), 3630 A. (ε 5500), and 3780 A. (ε 4270).

(e) 6-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*. The *azanthracene* (1 g.) was oxidised in the same manner as the 5-isomer. The *quinone* crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow needles (30 mg., m. p. 201—202°) (Found: C, 66·3; H, 3·7. $C_{15}H_{10}O_2NCl$ requires C, 66·2; H, 3·7%).

Attempted Synthesis of 7-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*.—4-(7′-*Hydroxy*-2′-*naphthylimino*)-*pentan*-2-*one*. 7-Hydroxy-2-naphthylamine (4·7 g.) was condensed with acetylacetone (7·0 c.c.) as usual, and the *product* crystallised from benzene to give white needles (6·6 g., m. p. 150—151°) (Found: C, 74·9; H, 6·3. $C_{15}H_{15}O_2N$ requires C, 74·7; H, 6·2%).

5′-*Hydroxy*-2 : 4-*dimethyl*-5 : 6-*benzoquinoline* (?). The pentanone (6 g.) was cyclised in 90% sulphuric acid, and the solution run into water and basified with sodium carbonate. The solid was collected, and crystallised from benzene in orange needles (4·6 g., m. p. 268—270°) (Found: C, 80·8; H, 5·8. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%). Ultra-violet absorption spectrum (0·000202M-solution in chloroform): Maxima at 3030 A. (inflexion) (ε 5250) and 3560 A. (ε 2570).

Synthesis of 8-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*.—(a) 8-*Amino*-2-*acetnaphthalide* was

obtained by reducing 8-nitro-2-acetnaphthalide (14·5 g.) in alcohol (400 c.c.) with etched iron, from iron filings (100 g.). It crystallised from benzene in colourless needles (10·5 g., m. p. 148—149°) (Found: C, 72·1; H, 6·1. $C_{12}H_{13}ON_2$ requires C, 72·0; H, 6·0%).

(b) 8-*Chloro*-2-*acetnaphthalide* was obtained from the amino-compound (10 g.) in the same manner as the 5-isomer. Crystallisation from dilute ethanol gave white microcrystals (8·5 g., m. p. 157—158°) (Found: C, 65·3; H, 4·3. $C_{12}H_{10}ONCl$ requires C, 65·5; H, 4·45%).

(c) On hydrolysis, the acetyl compound gave 8-*chloro*-2-*naphthylamine* (5 g.) as colourless needles from light petroleum (b. p. 60—80°); m. p. 69—70° (Found: C, 67·8; H, 4·4. $C_{10}H_8NCl$ requires C, 67·6; H, 4·5%).

(d) 4-(8′-*Chloro*-2′-*naphthylimino*)*pentan*-2-*one*. 8-Chloro-2-naphthylamine (3 g.) was condensed with acetylacetone, and the product crystallised from light petroleum (b. p. 60—80°) to give pale yellow needles (3·4 g., m. p. 72—73°) (Found: C, 69·2; H, 5·3. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

(e) 8-*Chloro*-2 : 4-*dimethyl*-1-*azanthracene*. The pentanone (3 g.) was cyclised as usual and the resulting *product* crystallised from benzene–light petroleum (b. p. 60—80°) to give colourless needles (2·1 g., m. p. 153°) (Found: C, 74·7; H, 4·7. $C_{15}H_{12}NCl$ requires C, 74·5; H, 4·9%). Ultra-violet absorption spectrum (0·000263M-solution in hexane): Maxima at 3200 A. (inflexion) (ε 1950), 3340 A. (inflexion) (ε 2750), 3480 A. (ε 3550), 3650 A. (ε 3470), and 3830 A. (ε 3310).

(f) 8-*Chloro*-2 : 4-*dimethyl*-1-*azanthraquinone*. The azanthracene (0·5 g.) was oxidised in the same manner as the 5-isomer. The *quinone* crystallised from benzene–light petroleum (b. p. 60—80°) in yellow needles (20 mg., m. p. 228—229°) (Found: C, 66·1; H, 3·55. $C_{15}H_{10}O_2NCl$ requires C, 66·2; H, 3·7%).

We thank Imperial Chemical Industries (Dyestuffs) Ltd. for a grant and facilities to one of us (N. L.).

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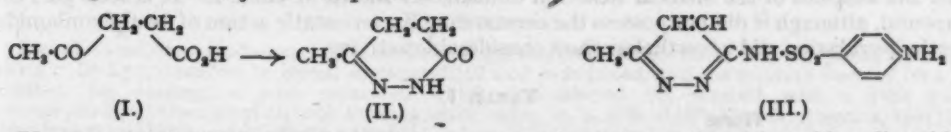
105. *The Conversion of Sucrose into Pyridazine Derivatives. Part II. 4-Amino-2-phenyl-6-methyl-3-pyridazone, 4-Amino-2-(p-nitrophenyl)-6-methyl-3-pyridazone, and their Sulphanilamido-derivatives.**

By W. G. OVEREND and L. F. WIGGINS.

The preparations of the sulphanilamido-derivatives of the new amino-pyridazones named in the title are described. The constitutions of some of the intermediates are established.

SULPHANILAMIDE derivatives having a diazine substituent on the N^4 group have come into prominence in recent years, owing largely to the fact that treatment of certain diseases by their aid seems to be accompanied by a particularly small degree of toxic effect. The diazines used, however, in the manufacture of these sulphanilamide derivatives are variously substituted pyrimidines and pyrazines; pyridazine derivatives seem to have been largely neglected.

We have therefore embarked on a study of the sulphanilamide and other derivatives of this type of compound. In Part I (this vol., p. 239) we described the preparation of 3-sulphanilamido-6-methylpyridazine and the intermediates required in its synthesis from lævulic acid, and showed that it possessed striking bacteriostatic power, so much so that against certain organisms it possessed greater activity than sulphathiazole.



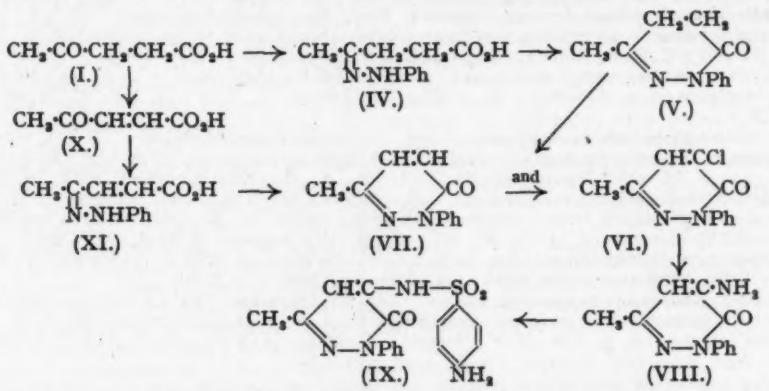
(I.) (II.) (III.)

The essential step in the synthesis of this compound was the condensation of lævulic acid (I) with hydrazine to form 6-methyl-3-pyridazinone (II) which, after several further transformations was converted into 3-sulphanilamido-6-methylpyridazine (III). Now we have prepared sulphanilamide derivatives from the condensation products of phenylhydrazine or *p*-nitrophenylhydrazine with lævulic acid.

Lævulic acid (I) when treated with phenylhydrazine yielded the corresponding phenylhydrazone (IV). On heating this at 160°, ring closure was effected, and the product was 2-phenyl-6-methyl-3-pyridazinone (V). This compound was prepared by Fischer (*Annalen*, 1886, **236**, 147) who referred to it as the anhydride of lævulic acid phenylhydrazone. On being treated with phosphorus pentachloride, this was converted into a mixture of 2-phenyl-6-methyl-3-pyridazone (VII) and 4-chloro-2-phenyl-6-methyl-3-pyridazone (VI), the latter in 60% yield and the former in very small yield. Ach (*ibid.*, 1889, **253**, 47), who first carried out this

* Patent applied for.

transformation, reported equal amounts. The yield of 4-chloro-2-phenyl-6-methyl-3-pyridazone could be further augmented, since it could be obtained by treating 2-phenyl-6-methyl-3-



pyridazone with phosphorus pentachloride. This experiment indicates that the mechanism of the reaction between (V) and phosphorus pentachloride is such that first a dehydrogenation occurs at C_4 and C_5 and subsequently chlorination takes place on C_5 to give (VI).

That the constitution of the pyridazone derivative obtained from 2-phenyl-6-methyl-3-pyridazinone was indeed represented by (VII), *i.e.*, with an unsaturated linkage between C_4 and C_5, has been proved by the fact that it is also obtained by cyclisation of the phenylhydrazone (XI) of β-acetylacrylic acid (X) which, of course, must possess αβ-unsaturation.

The conversion of 4-chloro-2-phenyl-6-methyl-3-pyridazone, proof of the constitution of which was afforded by Ach (*loc. cit.*), into *4-amino-2-phenyl-6-methyl-3-pyridazone* (VIII) was easily effected in 88% yield by treatment with methyl-alcoholic ammonia at 125—130°.

This amine formed only a *monohydrochloride*, and on acetylation with acetic anhydride and sodium acetate, it gave *4-acetamido-2-phenyl-6-methyl-3-pyridazone*, which did not form salts. On treating 4-amino-2-phenyl-6-methyl-3-pyridazone with *p*-acetamidobenzenesulphonyl chloride in pyridine solution 4-(p-*acetamidobenzenesulphonamido*)-2-*phenyl*-6-*methyl*-3-*pyridazone* was obtained which, on treatment with either 10% aqueous sodium hydroxide or with 2N-hydrochloric acid, was transformed into *4-sulphanilamido-2-phenyl-6-methyl-3-pyridazone* (IX), and this was reacetylated by means of acetic acid and acetic anhydride. Alternatively, the sulphanilamide derivative was obtained by condensation of the amine (VIII) with *p*-nitrobenzenesulphonyl chloride to form 4-(p-*nitrobenzenesulphonamido*)-2-*phenyl*-6-*methyl*-3-*pyridazone*, followed by its catalytic hydrogenation over Raney nickel.

The new sulphanilamide derivative was only slightly soluble in water (5·5 mg. per 100 c.c. of solution), but even so compares favourably in this property with sulphapyrazine and sulphathiazole. The results of the bacteriostatic tests on this sulphonamide (IX), carried out under the auspices of the Medical Research Council, are shown in Table I. It is seen that this compound, although it did not possess the outstanding bacteriostatic action of 3-sulphanilamido-6-methylpyridazine, did nevertheless show considerable activity.

TABLE I.

	Horse blood medium.	Synthetic medium.	Hartley's broth medium.					
Compound.	*Streptococcus hæmolyticus.*	*Escherichia coli.*	*Streptococcus hæmolyticus.*	*Escherichia coli.*	*Proteus vulgaris.*	*Pseudomonas aeruginosa.*	*Staphylococcus adreus.*	*Clostridium welchii.*
4-Sulphanilamido-2-phenyl-6-methyl-3-pyridazone	1·0	0·1	20	3	50	50	100	20
Sulphathiazole	0·3	0·03	15	5	10	5	100	5

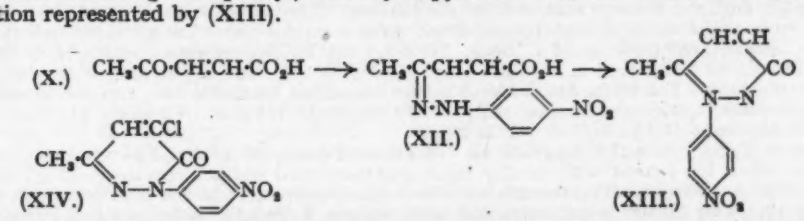
The figures represent mg. of compound per 100 c.c. of solution necessary to prevent growth of the organism.

4-Sulphanilamido-2-(p-nitrophenyl)-6-methyl-3-pyridazone was prepared from 2-(*p*-nitrophenyl)-6-methyl-3-pyridazinone by a series of reactions similar to those described above, *i.e.*,

by the condensation of lævulic acid with *p*-nitrophenylhydrazine, and also by an alternative procedure involving the nitration of 2-phenyl-6-methyl-3-pyridazinone according to the method of Fischer and Ach (*Annalen*, 1889, **253**, 59).

2-(*p*-Nitrophenyl)-6-methyl-3-pyridazinone, on treatment with an excess of phosphorus pentachloride at 160°, yielded 2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone* (XIII) and 4-*chloro*-2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone* (XIV) although the yield of the former was only about 4% of the theoretical. The reaction is completely analogous to that which takes place when 2-phenyl-6-methyl-3-pyridazinone is treated with an excess of phosphorus pentachloride.

The constitutions of the products (XIII) and (XIV) were proved as follows. β-Acetylacrylic acid (X) was converted into its *p*-nitrophenylhydrazone (XII). This when cyclised by heating gave a product identical with the halogen-free substance obtained from the reaction of phosphorus pentachloride with 2-(*p*-nitrophenyl)-6-methyl-3-pyridazinone; this must therefore have the constitution represented by (XIII).



Moreover, 2-phenyl-6-methyl-3-pyridazone (VII), the structure of which has been similarly proved by an analogous reaction, on nitration also yielded (XIII). Similarly 4-chloro-2-phenyl-6-methyl-3-pyridazone (VI), the structure of which had been proved by Ach (*Annalen*, 1889, **253**, 47) yielded on nitration a product identical with (XIV). Since in (XIII) and (XIV), the *p*-nitrophenyl grouping is pre-fixed, these results indicate that the rest of the molecule of (XIII) must have a structure similar to (VII), and that of (XIV) a structure similar to (VI).

4-Chloro-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone, on treatment at 120—130° with methyl alcohol saturated at 0° with ammonia gas, was converted into 4-*amino*-2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone*, which, in contrast to 4-amino-2-phenyl-6-methyl-3-pyridazone, did not form a salt. It was readily acetylated with acetic anhydride to form 4-*acetamido*-2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone*.

When the amino-derivative was condensed with *p*-acetamidobenzenesulphonyl chloride in dry pyridine solution, it yielded 4-(p-*acetamidobenzenesulphonamido*)-2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone*. This product was deacetylated by treatment with 10% aqueous sodium hydroxide solution to yield the free *sulphonamide*, reacetylated with dilute acetic acid and acetic anhydride. Both the acetyl derivative and the free sulphonamide had a very small solubility in water, that of the free sulphonamide being 0·8 mg. per 100 c.c. of solution at 15°. The sulphonamide was tested bacteriostatically against *Staphylococcus aureus*. It appeared to show some inhibitory effect on the growth of this organism, but it seemed that its solubility was too small to allow the attainment of a sufficiently concentrated solution for use in chemotherapy.

Experimental.

Lævulic Acid Phenylhydrazone.—The acid (10·91 g.) was dissolved in water (10 c.c.), phenylhydrazine (10 c.c.; 10·2 g.), dissolved in glacial acetic acid (10 c.c.), was added, and the mixture warmed for a few minutes. On cooling, a solid separated which was filtered off, washed with a little water, and recrystallised from ethyl alcohol, forming white cubes, m. p. 109—110° (Fischer, *Annalen*, 1886, **236**, 146, gives m. p. 108°); yield, 15·54 g.(80·9%).

2-*Phenyl*-6-*methyl*-3-*pyridazinone.*—Lævulic acid phenylhydrazone (6·37 g.) was heated at 160—165° for 3 hours. Thereafter the product was recrystallised from ethyl alcohol–water, forming colourless plates, m. p. 107° (Fischer, *ibid.*, p. 147, gives m. p. 106°); yield, 3·25 g. (56·5%) (Found: C, 70·4; H, 5·9; N, 15·2. Calc. for $C_{11}H_{12}ON_2$: C, 70·2; H, 6·3; N, 14·9%). It had a solubility in water at 15° of 0·53 g. per 100 c.c. of solution.

Treatment of 2-*Phenyl*-6-*methyl*-3-*pyridazinone with Phosphorus Pentachloride.*—The pyridazinone (15 g.) and phosphorus pentachloride (75 g.) were intimately mixed and then heated at 160°. A vigorous evolution of hydrogen chloride ensued. The mixture was allowed to cool, ice-water added to decompose excess of phosphorus pentachloride, and the product repeatedly extracted with boiling water. The extract was filtered and set aside for 24 hours. Crystals of 4-chloro-2-phenyl-6-methyl-3-pyridazone which separated were collected; they recrystallised from ethyl alcohol in long, shining white needles, m. p. 135—136° (Ach, *Annalen*, 1889, **253**, 47, gives m. p. 136°); yield, 9·9 g. (55·9%) (Found: C, 60·0; H, 4·5; Cl, 15·4. Calc. for $C_{11}H_9ON_2Cl$: C, 59·9; H, 4·1; Cl, 16·1%).

After removal of this pyridazone, the filtrate was concentrated, and excess of aqueous sodium hydroxide added. The mixture was extracted with ether, and the extract dried ($MgSO_4$). After removal of the solvent, a yellow oil remained which crystallised. It recrystallised from ligroin in white cubes, m. p.

79—80°, and was 2-phenyl-6-methyl-3-pyridazone (Ach, *loc. cit.*, gives m. p. 81°); yield, 0·5 g. (3·3%) (Found: C, 60·6; H, 5·4; N, 14·6. Calc. for $C_{11}H_{10}ON_2$: C, 60·9; H, 5·3; N, 15·0%).

Treatment of 2-Phenyl-6-methyl-3-pyridazone with Phosphorus Pentachloride.—The pyridazone (0·55 g.) and phosphorus pentachloride (2·5 g.) were mixed intimately and then heated at 160°. A fairly vigorous evolution of hydrogen chloride occurred. After being cooled, ice-water was added to destroy excess of phosphorus pentachloride, and the product extracted repeatedly with boiling water. The solid which separated on cooling the extract, was filtered off; it recrystallised from ethyl alcohol in colourless needles, m. p. alone or in admixture with 4-chloro-2-phenyl-6-methyl-3-pyridazone 135—136°; yield, 0·40 g. (61·6%).

4-Amino-2-phenyl-6-methyl-3-pyridazone.—4-Chloro-2-phenyl-6-methyl-3-pyridazone (5·01 g.) was heated in an autoclave at 125—130° for 24 hours with methyl alcohol (300 c.c.) saturated at 0° with ammonia. After cooling, the mixture was filtered and evaporated to dryness. The solid residue was hydrolysed by heating with baryta (1·5 equivs.; 8·16 g. of barium hydroxide in 75 c.c. of water) for 2 hours at 80° (this and subsequent operations were carried out in an atmosphere of nitrogen), and the solution thereafter evaporated to dryness. The dry residue was extracted with chloroform, the extract dried ($MgSO_4$), and the solvent removed by distillation. The syrup remaining was crystallised by trituration with ethyl alcohol, and recrystallised from acetone–water in colourless needles, m. p. 169°; yield, 3·96 g. (88%) (Found: C, 65·5; H, 5·2. $C_{11}H_{11}ON_3$ requires C, 65·6; H, 5·5%). This *pyridazone* (0·1 g.) was dissolved in absolute ethyl alcohol (5 c.c.), and dry hydrogen chloride bubbled through the solution. The white *hydrochloride* which separated was collected, and recrystallised from ethyl alcohol–ether in colourless cubes, m. p. 176° (decomp.) (Found: C, 55·5; H, 5·4; Cl, 14·9. $C_{11}H_{12}ON_3Cl$ requires C, 55·5; H, 5·1; Cl, 15·3%).

4-Acetamido-2-phenyl-6-methyl-3-pyridazone.—4-Amino-2-phenyl-6-methyl-3-pyridazone (1·00 g.) was boiled under reflux for ½ hour with freshly fused and powdered sodium acetate (0·43 g.) and acetic anhydride (16 c.c.). After cooling, the mixture was poured into water and the solid (A) which separated was filtered off. The filtrate was neutralised with sodium hydrogen carbonate and extracted with chloroform. The extract was dried ($MgSO_4$), and the solvent removed by distillation. The solid remaining was combined with solid (A) and recrystallised from ethyl alcohol–chloroform in shining white plates, m. p. 265°; yield, 1·22 g. (quantitative) (Found: C, 64·4; H, 5·6; N, 16·9. $C_{13}H_{13}O_2N_3$ requires C, 64·2; H, 5·4; N, 17·2%).

4-(N-Acetylsulphanilamido)-2-phenyl-6-methyl-3-pyridazone.—4-Amino-2-phenyl-6-methyl-3-pyridazone (1·8 g.) was dissolved in dry pyridine (20 c.c.), and *N*-acetylsulphanilyl chloride (1·1 mol.; 2·32 g.), also dissolved in dry pyridine (20 c.c.), was added. The mixture was stirred and kept at 45° for ½ hour. A solution of sodium hydroxide (0·35 g., 1 mol.) in water (120 c.c.) was added, and the pyridine removed by distillation under diminished pressure. The solid which separated was collected, and recrystallised from acetic acid–water in colourless cubes, m. p. 254°; yield, 1·64 g. (46%) (Found: C, 57·3; H, 4·8; N, 13·8. $C_{19}H_{18}O_4N_5S$ requires C, 57·3; H, 4·5; N, 14·1%).

4-Sulphanilamido-2-phenyl-6-methyl-3-pyridazone.—(a) 4-(*N*-Acetylsulphanilamido)-2-phenyl-6-methyl-3-pyridazone (0·169 g.) was heated under reflux for 45 minutes with 10% aqueous sodium hydroxide solution (10 c.c.). After cooling, the mixture was neutralised with dilute hydrochloric acid, and a white solid separated. This was collected, and recrystallised from ethyl alcohol–water in shining white plates, m. p. 178°; yield, theoretical [Found: C, 57·6; H, 4·6; N, 15·9; $-NH_2$ (by nitrite titration), 4·3. $C_{17}H_{16}O_3N_4S$ requires C, 57·3; H, 4·5; N, 15·7; $-NH_2$, 4·4%].

(b) The material (0·1427 g.) was boiled under reflux for one hour with 2N-hydrochloric acid (10 c.c.). On cooling, the mixture was neutralised with aqueous sodium hydroxide solution; the flocculent white solid which separated was collected. After recrystallisation from acetic acid–water it had m. p. 178° alone or in admixture with 4-sulphanilamido-2-phenyl-6-methyl-3-pyridazone; yield, 0·102 g. (78%).

Reacetylation.—This sulphanilamido-pyridazone (0·03 g.) was mixed with dilute acetic acid (2 c.c.) and acetic anhydride (2 c.c.). The mixture was kept overnight and then poured into water. The solid which separated was collected, and recrystallised from acetic acid–water in white cubes, m. p. 253—254° alone or in admixture with the above acetyl compound; yield, 0·017 g. (53%).

4-(p-Nitrobenzenesulphonamido)-2-phenyl-6-methyl-3-pyridazone.—4-Amino-2-phenyl-6-methyl-3-pyridazone (0·57 g.) was dissolved in dry pyridine (10 c.c.), *p*-nitrobenzenesulphonyl chloride (1·1 mols.; 0·682 g.), also dissolved in dry pyridine, was added, and the mixture kept at room temperature overnight. When this was poured into water containing sodium hydroxide (0·113 g.) a solid separated which was filtered off. Concentration of the filtrate yielded a further quantity of crystals. The combined products recrystallised from ethyl alcohol–water in colourless needles, m. p. 87°; yield, 0·25 g. (25%) (Found: C, 52·2; H, 3·2. $C_{17}H_{14}O_5N_4S$ requires C, 52·8; H, 3·6%).

Reduction.—This *compound* (0·25 g.) was dissolved in dry methyl alcohol (100 c.c.) and hydrogenated at room temperature over Raney nickel. The solution was filtered and evaporated to dryness. The residue was dissolved in hot ethyl alcohol–water and filtered (charcoal). On cooling, crystals were deposited, which were collected and recrystallised from ethyl alcohol-water in white plates, m. p. alone or in admixture with 4-sulphanilamido-2-phenyl-6-methyl-3-pyridazone 178°; yield, 0·07 g. (30·5%).

Lævulic Acid p-Nitrophenylhydrazone.—The acid (2·3 g.), dissolved in water (10 c.c.), was mixed with *p*-nitrophenylhydrazine (3·02 g.) dissolved in glacial acetic acid (3·02 c.c.), and the solution warmed. On cooling, a solid separated which recrystallised from ethyl alcohol–water in orange needles, m. p. 207—208° (Fischer and Ach, *Annalen*, 1889, **253**, 61, state that this hydrazone sinters and decomposes at about 190°); yield, 4·38 g. (89·4%) (Found: C, 53·0; H, 5·2. Calc. for $C_{11}H_{13}O_4N_3$: C, 52·6; H, 5·2%).

2-(p-Nitrophenyl)-6-methyl 3-pyridazinone.—The foregoing *p*-nitrophenylhydrazone (21 g.) was heated under diminished pressure on an oil-bath at the m. p. for 0·75 hour. The product, which crystallised on trituration with ethyl alcohol, was recrystallised from ethyl alcohol-water, affording yellow needles, m. p. 118°; yield, 12·7 g. (65·9%) (Found: C, 56·2; H, 4·7; N, 18·2. $C_{11}H_{11}O_3N_3$ requires C, 56·6; H, 4·7; N, 18·0%). This *compound* had a solubility in water at 15° of 0·1 g. per 100 c.c. of solution.

Treatment with phosphorus pentachloride. This pyridazinone (5·0 g.) and phosphorus pentachloride

(25 g.) were mixed intimately and heated to 160°, hydrogen chloride being evolved. The mixture was allowed to cool, and crushed ice added to destroy excess of phosphorus pentachloride. The product was extracted repeatedly with boiling ethyl alcohol–water and, on cooling, a yellow solid (A) separated. This recrystallised from acetone in white needles, m. p. 217—218°, and was shown to be *4-chloro-2-(p-nitrophenyl)-6-methyl-3-pyridazone*; yield, 2·0 g. (36%) (Found: C, 49·2; H, 3·2; Cl, 13·2. $C_{11}H_8O_2N_3Cl$ requires C, 49·7; H, 3·0; N, 13·3%).

The mother-liquors after separation of the solid (A) were concentrated, excess of aqueous potassium hydroxide was added, and the mixture extracted with ether. The extract was dried ($MgSO_4$), and the solvent removed by distillation. The solid (B) remaining recrystallised from acetone–water in white plates, m. p. 184—185. This compound was shown to be 2-(p-*nitrophenyl*)-6-*methyl*-3-*pyridazone*; yield, 0·18 g. (3·7%) (Found: C, 56·6; H, 4·1; N, 18·1. $C_{11}H_9O_3N_3$ requires C, 57·1; H, 3·9; N, 18·2%).

4-Amino-2-(p-nitrophenyl)-6-methyl-3-pyridazone.—4-Chloro-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone (0·62 g.) was heated in an autoclave at 120—130° for 24 hours with methyl-alcoholic ammonia (300 c.c.) (saturated at 0°). The resultant solution was filtered and evaporated to dryness. The residue was treated with baryta (1·5 equivs.; 0·3 g. of hydroxide in 50 c.c. of water) at 80° in an atmosphere of nitrogen, and the product, after being evaporated to dryness, was extracted with boiling chloroform. The extract, after being dried ($MgSO_4$), was evaporated to dryness, and the product recrystallised from ethyl alcohol in small yellow needles, m. p. 196°; yield, 0·25 g. (44·2%) (Found: C, 53·7; H, 4·4. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1%).

Acetyl derivative. The foregoing compound (0·1 g.), fused and powdered sodium acetate (0·04 g.), and acetic anhydride (5 c.c.) were boiled under reflux for ½ hour. After cooling, the mixture was poured into water, and the precipitate filtered off; it recrystallised from ethyl alcohol–water in colourless plates, m. p. 190—191°; yield, quantitative(Found: C, 53·8; H, 4·7. $C_{13}H_{12}O_4N_4$ requires C, 54·1; H, 4·2%).

4-(N-Acetylsulphanilamido)-2-(p-nitrophenyl)-6-methyl-3-pyridazone.—The above amine (1·27 g.) was dissolved in dry pyridine (25 c.c.), *N*-acetylsulphanilyl chloride (1·1 mols.; 1·35 g.), also dissolved in dry pyridine (10 c.c.), was added, and the mixture kept at 45° for ½ hour. A solution of sodium hydroxide (0·21 g.; 1 mol.) in water (100 c.c.) was added, and the pyridine distilled off under diminished pressure. The solid which separated was filtered off; it recrystallised from acetic acid–water in yellow needles, m. p. 238°; yield, 1·0 g.(45·4%) (Found: C, 51·4; H, 3·8. $C_{19}H_{17}O_6N_5S$ requires C, 51·5; H, 3·8%).

Hydrolysis. This *acetylsulphanilamido*-compound (0·30 g.) was boiled under reflux for 45 minutes with 10% aqueous sodium hydroxide solution (10 c.c.), and the mixture allowed to cool, and neutralised with dilute hydrochloric acid. The resulting *sulphanilamido*-compound was filtered off and recrystallised from ethyl alcohol–water in yellow plates, m. p. 190; yield, 0·12 g. (44·4%) [Found: C, 51·5; H, 3·3; $-NH_2$ (by nitrite titration), 3·8. $C_{17}H_{15}O_4N_5S$ requires C, 50·8; H, 3·7; $-NH_2$, 3·9%].

Reacetylation. The last compound (0·005 g.), dilute acetic acid (2 c.c.), and acetic anhydride (2 c.c.) were mixed, and the mixture kept overnight. When this was poured into water (100 c.c.), a solid separated, which recrystallised from acetic acid–water, m. p. 238° alone or in admixture with 4-(*N*-acetylsulphanilamido)-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone; yield quantitative.

Nitration of 2-Phenyl-6-methyl-3-pyridazinone.—The pyridazinone (2·0 g.) and fuming nitric acid (14 c.c.) were mixed at 0° and kept for one hour. The mixture was poured into water, and the solid which separated was collected and recrystallised from ethyl alcohol in yellow needles, m. p. 117° alone or in admixture with 2-(*p*-nitrophenyl)-6-methyl-3-pyridazinone; yield, 1 g. (40%).

Nitration of 2-Phenyl-6-methyl-3-pyridazone.—The pyridazone (0·5 g.) was cooled to 0° in an ice-bath, fuming nitric acid (5 c.c.) added, and the mixture kept at 0° for an hour. On being poured into water, this yielded a solid which, after recrystallising from ethyl alcohol–water in colourless needles, had m. p. 184° alone or in admixture with 2-(*p*-nitrophenyl)-6-methyl-3-pyridazone; yield 0·56 g. (95%).

Nitration of 4-Chloro-2-phenyl-6-methyl-3-pyridazone.—This pyridazone (0·49 g.) was similarly nitrated; the resulting flocculent white solid recrystallised from ethyl alcohol–water in flocculent white needles, m. p. 218° alone or in admixture with 4-chloro-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone; yield quantitative.

Nitration of 4-Amino-2-phenyl-6-methyl-3-pyridazone.—Similarly, from this pyridazone (0·61 g.) and fuming nitric acid (10 c.c.) was obtained a yellow solid which, recrystallised from absolute ethyl alcohol, had m. p. 196° alone or in admixture with 4-amino-2-(*p*-nitrophenyl)-6-methyl-3-pyridazone; yield, 0·43 g. (60·6%).

β-Acetylacrylic Acid Phenylhydrazone.—This hydrazone, prepared by the usual method and recrystallised from ethyl alcohol, formed yellow needles, m. p. 160° (Wolff, *Annalen*, 1891, **264**, 251, quotes m. p. 160°) (Found: C, 64·4; H, 5·9. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·6; H, 5·9%).

Thermal decomposition. The hydrazone (1·0 g.) was heated at its m. p. for 2 hours. The residue was dissolved in ethyl alcohol, and the solution filtered (charcoal). After removal of solvent, the residue recrystallised from ligroin in white cubes, m. p. 79—80° alone or in admixture with 2-phenyl-6-methyl-3-pyridazone; yield, 0·5 g. (55%).

β-Acetylacrylic Acid p-Nitrophenylhydrazone.—This *hydrazone*, prepared by normal methods and recrystallised from ethyl alcohol–water, formed yellow needles, m. p. 220—221°; yield, 3·17 g. (39%) (Found: C, 52·8; H, 3·9; N, 16·8. $C_{11}H_{11}O_4N_3$ requires C, 53·0; H, 4·4; N, 16·9%).

Thermal decomposition. The *p*-nitrophenylhydrazone (2·13 g.) was heated in a vacuum at 180° for 4 hours. White crystals sublimed and were collected at the top of the flask; they recrystallised from ethyl alcohol–water in white needles, m. p. 183—184° alone or in admixture with 2-(*p*-nitrophenyl)-6-methyl-3-pyridazone; yield, 1·0 g. (50%).

Attempted Cyclisation of Ethyl β-Acetylacrylate Phenylhydrazone.—The phenylhydrazone (m. p. 117°; Bender, *Ber.*, 1888, **21**, 2493, gives m. p. 117°) (1·02 g.) was heated at 110° under diminished pressure for 3 hours. The product solidified on cooling, and was extracted with ligroin. The extract was evaporated to dryness, and the residue recrystallised from ligroin in white cubes, m. p. alone or in admixture with 2-phenyl-6-methyl-3-pyridazone, 79—80°; yield, 0·1 g. The residue remaining from the ligroin extraction was shown to be unchanged starting material (0·8 g.).

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106. *An X-Ray and Thermal Examination of the Glycerides. Part VIII. Glycerides of Erucic, Brassidic, Oleic, and Elaidic Acids.*

By M. G. R. CARTER and T. MALKIN.

The α-monoglycerides and αα′-diglycerides of erucic, brassidic, oleic, and elaidic acids, and the triglycerides of erucic, brassidic, and elaidic acids are found to exhibit the same type of polymorphism as the corresponding saturated compounds. The *X*-ray examination reveals an interesting difference in structure between the *cis*- and the *trans*-compounds, which appears to be general for long-chain compounds.

Some observations are made on the misleading *X*-ray data for α-monoglycerides reported by Filer, junr., Sidhu, Daubert, and Longenecker.

RESUMING our study of the glycerides, interrupted in 1939, we have now completed our examination of the α-monoglycerides, αα′-diglycerides, and the simple triglycerides of oleic and erucic acids and their geometric isomers, elaidic and brassidic acids.

Although in their melting phenomena and polymorphism these compounds show no marked differences from the corresponding glycerides of saturated acids, yet a most interesting difference between the derivatives of *cis*- and *trans*-acids is revealed by the *X*-ray results.

It has been shown in Parts I, II, and III (*J.*, 1934, 666; 1936, 1628; 1937, 1409) that mono-, di-, and tri-glycerides each give rise to a distinctive diffraction pattern, referred to in this field as " side spacings ", and it is now found that, whilst glycerides of *trans*-unsaturated acids give rise to the same type of side spacings as their saturated analogues, derivatives of *cis*-acids give quite different spacings. The same distinction holds for simpler *cis-trans*-isomers, *e.g.*, erucic and brassidic acids, and it would seem, in general, that saturated and *trans*-olefinic chains pack together in a similar manner, which differs from the arrangement of *cis*-chains.

This is not altogether surprising, as it is seen at once from a model that, whilst a *trans*-bond causes no appreciable change in the alinement of the hydrocarbon chain, a *cis*-bond brings about a decided change, thus :

The above differences in side spacings will be clear from the *X*-ray photographs in Plates I and II.

It is hoped to pursue the more general implications of the above observations, but of immediate interest is their bearing on the structure of β-oleodistearin recently proposed by Filer, jun., Sidhu, Daubert, and Longenecker (*J. Amer. Chem. Soc.*, 1946, **68**, 169) and Lutton (*ibid.*, p. 676). These authors find a long spacing greater than the maximum length of a single molecule, and propose respectively structures (I) and (II) which differ from the more compact structure (III) proposed by Clarkson and Malkin (Part I, *loc. cit.*) for simple triglycerides.

Our own unpublished long spacing for β-oleodistearin agrees with that of Lutton, whose proposed structure (II) finds additional support in our present results. Thus, structure (III), surrounded by similar units, would require, in the case of β-oleodistearin, a non-linear chain to be packed between four straight chains, which appears less likely than structures (II), where the oleic chains are adjacent. Arising out of this is the interesting case of β-elaidydistearin, where the unsaturated chain is linear, and which might therefore be expected to have the same structure as tristearin, (III).

Numerous long spacings which could not be satisfactorily explained on the basis of structure (III) have been reported in Parts VI and VII of this series (*J.*, 1939, 1143, 1521) which deal with mixed glycerides of acids differing by at least four carbon atoms, and it is probable that

Behenic acid (*saturated*).

Brassidic acid (trans).

Erucic acid (cis).

α-*Monoelaidin* (trans).

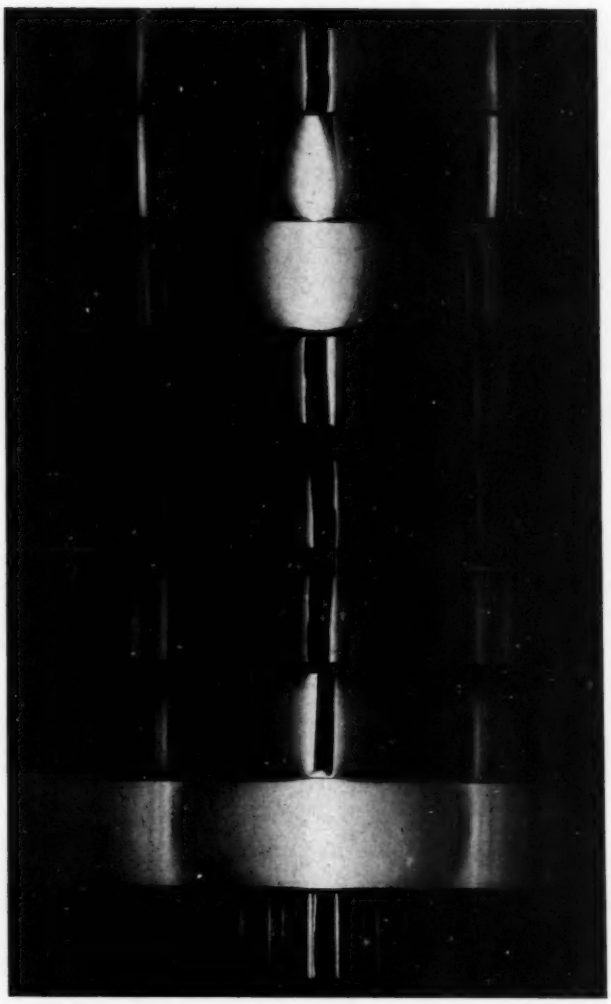
α-*Monostearin*.

α-*Monopalmitin*.

α-*Monoerucin* (cis).

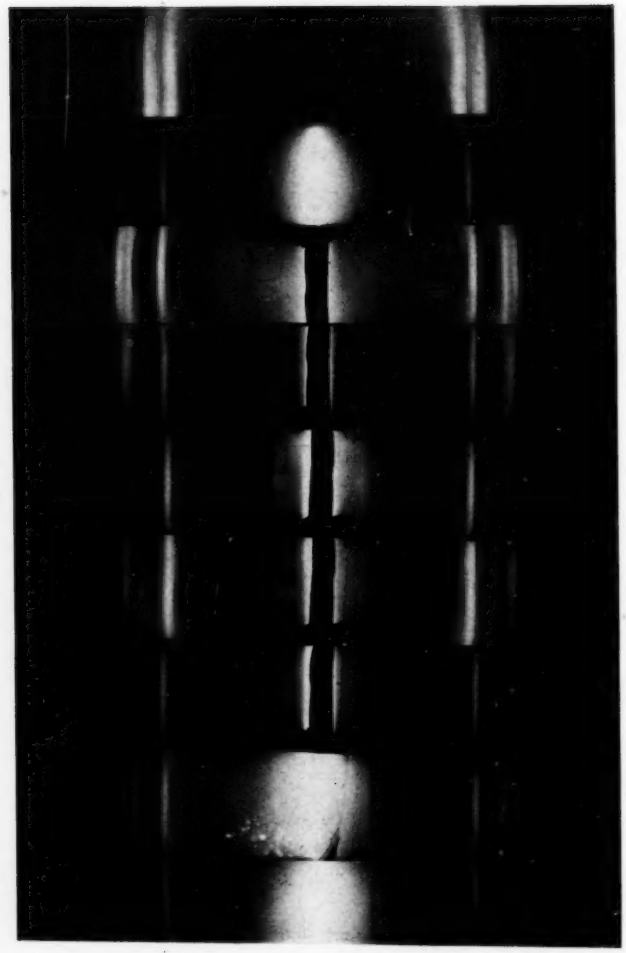
α-*Mono-olein* (cis).

α-*Monoelaidin* (*long spacing*).



[*To face p.* 554.

PLATE II.



α-Monoelaidin (circular camera).

αα′-Dipalmitin (β).

αα′-Dibrassidin (β).

αα′-Dibrassidin (β′).

αα′-Dierucin (β′).

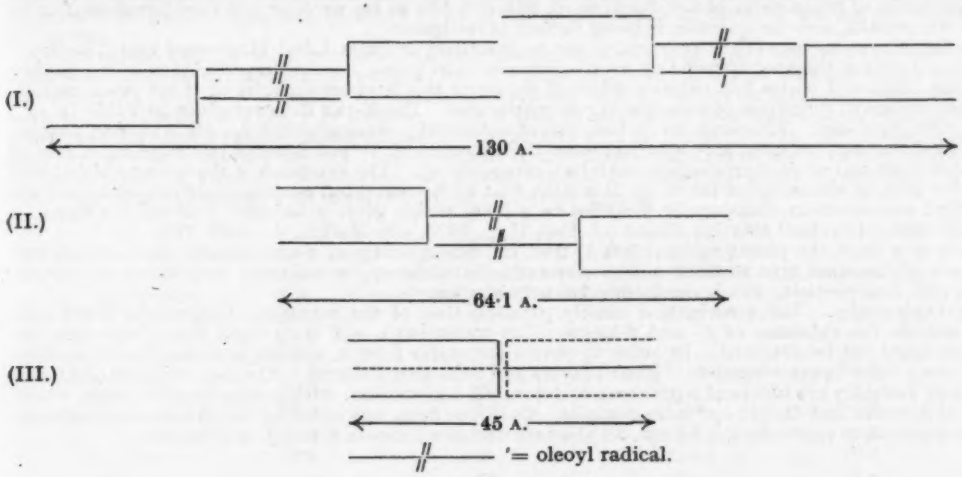
αα′-Dierucin (β).

Trierucin.

Trielaidin.

Tristearin.

certain of these are arranged as in structure (II), although in these cases the problem is complicated by the possibility of interpenetration of the chains of unequal length.



Experimental.

Thermal Investigation.—This was carried out by means of cooling and heating curves, and capillary m. p. experiments (as described in Parts I, II, and III, *locc. cit.*) for saturated glycerides. M. p.'s of the various polymorphic forms are given in Table I.

Table I.

	Vitreous.	α.	β′.	β.	Lit. m. p.'s.
α-*Monoerucin*	15°	36°	47°	50°	
α-*Monobrassidin*	37	62	68·5	71	
α-Mono-olein	12·5	25	32	35	35 [1]; 26—27, 35 [2]; 35·5 [3]
α-Monoelaidin	29·5	42	56	58·5	58·5 [4]
αα′-Dierucin	—	41	44·5	46·5	47 [5]
αα′-Dibrassidin	—	63·5	66·5	68·5	65 [5]
αα′-Diolein	—	18	—	25	
αα′-*Dielaidin*	—	49	58	55	
Trierucin	6	17	25	30	31 [6]
Tribrassidin	43	50	—	59	36, 47 [4]; 57 [7]
Trielaidin	15·5	37	—	42	38 [8]; 16·6, 42·0 [9]

[1] Krafft, *Ber.*, 1903, **36**, 4343. [2] Täufel and Künkel, *Fettchem. Umschau*, 1935, **42**, 27. [3] Daubert, Fricke, and Longenecker, *J. Amer. Chem. Soc.*, 1943, **65**, 2142. [4] Filer, junr., Sidhu, Daubert, and Longenecker, *ibid.*, 1944, **66**, 1333. [5] Reimer and Will, *Ber.*, 1886, **19**, 3322. [6] *Idem*, *Ber.*, 1887, **20**, 2386. [7] Stohmann and Langbein, *J. pr. Chem.*, 1890, **42**, 372. [8] Duffy, *Jahresber.*, 1852, 511. [9] Filer, Sidhu, Daubert, and Longenecker, *loc. cit.*

Comparison of the above data with those given for the saturated mono-, di-, and tri-glycerides in Parts I, II, and III shows the closest parallel in the polymorphism. The heating and cooling curves now obtained are very similar to those obtained for the saturated compounds, and the general discussions of results in the thermal sections of the above papers hold, so that only a brief summary of the present results is necessary.

α-*Monoglycerides.* The upper and the lower curve in Fig. 1, Part II, are practically identical in form with those of α-monobrassidin and α-monoerucin, respectively. In the case of the latter, the transitions, vitreous → α, α → β′, β′ → β, take place at room temperature, and according to the duration of the cooling curve, arrests for α- and β′-forms may or may not appear on the heating curves (cf. curves, *A*, *B*, *C*, *D*, *E*, Fig. 1, Part II). The slowest change in this series is the transition β′ → β, and unless the curves are taken very slowly the highest m. p. observed is that of the β′-form.

αα′-*Diglycerides.* Here again the curves are similar to that given in Fig. 1, Part III. The cooling curve shows one arrest (melt → α-form), and the heating curve shows usually one (m. p. of β′-form), with occasionally a smaller higher arrest (m. p. of β-form). The transition α → β′ takes place rapidly in the solid state, and therefore the α m. p. is not observed on the heating curves, except in the case of dibrassidin, after very rapid cooling. The transition β′ → β is again very slow, and it is usually necessary to hold the β′-form near its m. p. for some time, to bring about conversion into the stable β-form.

Triglycerides. Cooling curves for all three are similar. They fall to the region of the vitreous m. p., whereat crystallisation sets in with marked rise in temperature to the m. p. of the α-form, if the cooling gradient is not too steep. With very steep cooling gradients, this conversion into α-forms is prevented, and solidification in the vitreous form sets in. Heating curves differ slightly from those of saturated

triglycerides, owing to the greater speed of the transition $\alpha \rightarrow \beta$ (in the case of trierucin $\alpha \rightarrow \beta'$), and no arrest corresponding to the α m. p. was observed. These curves show one arrest for tribrassidin and trielaidin (β m. p.) and two for trierucin (β' and β m. p.'s). There is some slight suggestion in the heating curve of tribrassidin of a β'-form, m. p. 56—57°, but so far we have not found confirmation in the *X*-ray results, and the question is being further investigated.

X-Ray Examination.—This was carried out as described in Parts I and II, pressed and "melted" layers and rods of the specimens being used. Since our last paper, notable improvement in the quality of *X*-ray films and plates has reduced times of exposure to about one-quarter of those given earlier, and has improved definition of side spacings in particular. The *X*-ray data are given in Table II.

α-Monoglycerides. Although, as in the case of saturated α-monoglycerides, only one long spacing was found for each member, side spacings show the existence of β'- and β-forms (obtained from rods of solidified melt and solvent-crystallised material, respectively). The existence of the α-forms is deduced from the general similarity of the m. p. data with that of the saturated α-monoglycerides, and from the fact that α-mono-olein occasionally solidifies in a form which gives a uniaxial interference figure, a characteristic of vertical rotating chains (cf. Part II, p. 1633, also Malkin, *J.*, 1935, 726).

It is seen from the photographs (Plate I) that the side spacings of α-monoelaidin and α-monobrassidin are of the same type as those of α-monostearin, but differ quite markedly from those of α-monoerucin and α-mono-olein, which are themselves very similar.

αα'-Diglycerides. The examination closely parallels that of the saturated diglycerides (Part III), and confirms the existence of β'- and β-forms. The transition $\alpha \rightarrow \beta'$ is so rapid that *X*-ray data for α-forms could not be obtained. In order to obtain the stable β-form, specimens should be crystallised very slowly from hexane–benzene. Melted layers and rods give β'-forms. The side spacings of dibrassidin and dielaidin are identical with those of saturated diglycerides, within experimental error, whilst those of dierucin and diolein are more complex. Only one form was obtained for diolein, and although the data probably represent the β-form, an absolute decision between β and β' is difficult.

TABLE II.

	Long spacings, A.			Side spacings, A.*	
	α.	β'.	β.	β'.	β.
α-Monoerucin	—	—	58·3	4·65 (s), 4·3, 4·05, 3·87, 3·68	4·57 (s), 4·33 (m), 4·08, 3·9, 3·75, 3·61
α-Monobrassidin	—	—	58·8	4·14 (s), 3·9, 3·75, 3·59	4·56 (s), 4·4, 4·15, 3·93 (s)
α-Mono-olein	—	—	49·5	—	4·58 (s), 4·32 (ms), 4·05, 3·77, 3·58
α-Monoelaidin	—	—	50·3	4·13 (s), 3·88, 3·73, 3·59	4·55 (s), 4·38, 4·14, 3·93 (s)
α-Monostearin for comparison	—	58·3	50·0	—	4·58 (s), 4·37, 4·12, 3·88 (s) †
αα'-Dierucin	—	47·8	46·4	4·68 (s), 4·24, 4·04, 3·85 (m), 3·66 (m), 3·49, 3·32	4·7 (s), 4·38, 4·28, 4·05 (m), 3·95 (ms), 3·64 (m), 3·49
αα'-Dibrassidin	—	58·8	63·1	4·59 (s), 4·0, 3·75 (s), 3·57	4·6 (s), 3·91 (s), 3·72 (s)
αα'-Diolein	—	—	39·7	—	4·7 (s), 4·44 (m), 4·23, 4·06 (m), 3·85 (ms), 3·64
αα'-Dielaidin	—	49 8	52·6	4·61 (s), 3·95, 3·75 (s), 3·6	4·6 (s), 3·9 (s), 3·7 (s)
αα'-Distearin, for comparison	—	—	49·5	—	4·6 (s), 3·9 (s), 3·73 (s)
Trierucin	—	54·7	51·1	4·53 (m), 4·28 (m), 4·07, 3·88 (m)	5·24, 4·6 (s), 4·03, 3·84, 3·7
Tribrassidin	59·3	—	53·6	—	5·3, 4·6 (s), 3·9 (m), 3·7 (m)
Trielaidin	—	—	44·1	—	5·3, 4·6 (s), 3·9 (m), 3·7 (m)
Tristearin, for comparison	50·6	—	45·0	—	5·3, 4·6 (s), 3·9 (m), 3·7 (m)

* s = strong; m = moderate. Other side spacings weak. Long spacings are accurate to $\simeq$ 0·2A., and side spacings, because of the diffuse lines, cannot be regarded as more accurate than to 0·03—0·04 A.

† With the better definition we are now getting, we consider these values more accurate than our earlier ones, which were slightly high.

Triglycerides. The data for the stable β-forms were obtained from pressed layers and rods. Melted layers gave the α-form for tribrassidin and the β'-form for trierucin. In the case of trielaidin, the transition $\alpha \rightarrow \beta$ was so rapid at room temperature that melted layers gave only the β-form. The long spacing of the α-form has, however, been reported recently by Filer, Sidhu, Daubert, and Longenecker (*loc. cit.*, 1946), working at low temperatures. They found 44·8 A. for the β-form and 48·0 A. for the α-form. Here again the side spacings of tribrassidin and trielaidin are identical with those of saturated simple triglycerides (Part I), whilst those of trierucin are different.

In their reported *X*-ray examination of α-monoglycerides, Filer, Sidhu, Daubert, and Longenecker (*J. Amer. Chem. Soc.*, 1944, **66**, 1333) stated that "powder diffraction data suitable for the identification of synthetic glycerides are not available in the literature": in view of this astonishing statement, it is pertinent to point out that in the present series of papers, *X*-ray data, which readily establish identity, have been reported for some *eighty* synthetic glycerides. The authors then continued with an account of their investigation of α-monoglycerides, which is mainly a repetition of the results and deductions of

Malkin and Shurbagy (*loc. cit.*), the only new feature of which is an extensive table of diffraction data, termed " Interplanar Spacings ", which they consider superior to the data of Malkin and Shurbagy for identification purposes. Their data differ from the latter in that (*a*) the number of values is unusually large, and (*b*) the side spacings, contrary to all previous experience in the field, are not distinctive for the series.

With regard to (*a*), it is at once obvious that this profusion of data is due mainly to the use of non-homogeneous *X*-rays, and that the authors, not realising this, have calculated all their values with the wave-length Cu-K_α, $\gamma = 1{\cdot}5386$ A., whereas approximately half the values should have been calculated with the wave-length Cu-K_β, $\gamma = 1{\cdot}389$ A. This is well illustrated by their long-spacing data given for α-monoelaidin (upper figures in their table) reproduced in Col. 2, Table III. In the third column we give the order of reflection and the type of radiation, and after correction of the β values, by dividing by the ratio of the α and β wave-lengths, *i.e.*, 1·5386/1·389 = 1·11, they are found, as expected, to be in good numerical agreement with the corresponding α values (col. 4).

TABLE III.

Intensity.	*d*/*n*.	Order of reflection (*n*), and type of radiation.	*d*/*n*,* β values (corr.).	*d*, long spacing, in A.
s	25·5	2α	25·5	51·0
w	21·1	—	—	—
w	19·1	3β	17·2	51·6
vw	17·6	—		
s	17·1	3α	17·1	51·3
vw	13·4	4β	12·1	48·4
s	12·6	4α	12·6	50·4
vw	11·3	5β	10·2	51·0
vw	10·4	5α	10·4	52·0
vw	9·19	6β	8·28	49·68
w	8·95	—		
m	8·36	6α	8·36	50·16
vw	6·88	8β	6·2	49·6
m	6·79	—		
m	6·19	8α	6·19	49·52
w+	5·64	10β	5·07	50·7
w	5·24	—		
w+	4·94	10α	4·94	49·4

* It will be appreciated that these values are merely *n*th order reflections of the long spacing (*d*). Without appropriate indices (002, 003, 004, etc.) their description as interplanar spacings is somewhat ambiguous, and tends to obscure the relationship between the length of the molecule and the long spacing.

We know of no satisfactory explanation for the remaining five values in the second column. Our own photographs give no evidence of these, but it is possible that at least two are due to the use of nylon capillary tubes for mounting the specimen. Nylon, a long-chain polymer, is known to give a long spacing of 17·4 A. and side spacings of 3·7 and 4·4 A. (cf. Baker and Fuller, *J. Amer. Chem. Soc.*, 1942, **64**, 2399). The values 17·6 and 8·95 might well be first and second orders of this long spacing.

With regard to the side spacings reported by Filer *et al.* (the lower values in their table), our objection lies in the quantity and the variability of the data. It has been shown in Part II (*loc. cit.*) that all the saturated α-monoglycerides from monodecoin to monostearin give two identical strong side spacings; *e.g.*, the photographs of α-monopalmitin and α-monostearin, reproduced in Plate I, are indistinguishable, whereas Filer *et al.* report seven and four strong side spacings, respectively.

Here again, the use of non-homogeneous *X*-rays, and probably the use of nylon, increases the number of lines; but further, some error enters into their intensity estimation. Thus, in the above two photographs, the two accompanying weaker lines (4·38 and 4·14 A.), between the two strong lines, are denoted as strong, and a still more glaring case is that of α-monoelaidin, Plate II, where the faint line furthest out from the centre (2·46 A.), which is barely visible, is stated to have the same intensity as the second of the strong lines (3·96 A.).

From the above it will be seen that the data of Filer and his co-workers only serve to confuse a sufficiently complicated field. Their mass of data, even when accurately calculated, is unnecessary for purposes of identification, for the long spacing and the characteristic side spacings suffice. It is only when the question of structure arises that additional data and accurate intensity relationships are of value.

Preparation of Glycerides.—The erucic and oleic acids used were Fraenkel and Landau's purest, the former purified by fractionation of the ester and subsequent crystallisation of the acid, and the latter by low-temperature crystallisation from acetone (cf. Brown and Shinowara, *J. Amer. Chem. Soc.*, 1937, **59**, 6; Smith, *J.*, 1939, 974). Brassidic and elaidic acid were made by the standard nitrous acid method as follows (cf. Rankoff, *J. pr. Chem.*, 1931, **131**, 293): *Brassidic acid.* 10 G. of erucic acid were added to a mixture of 75 c.c. of concentrated nitric acid and 175 c.c. of water, in a beaker, and the mixture heated to 50—55° on a water-bath. 2 G. of finely powdered sodium nitrite were slowly added, with stirring, and after a short time the molten layer gradually solidified as it was converted into brassidic acid. The aqueous acid was decanted from the solid cake, which was clarified two or three times over fresh distilled water. After crystallisation from alcohol, the yield was 7·5 g., m. p. 59·5°. *Elaidic acid.*

This was made in exactly the same manner except that the reaction temperature was 35—40°; yield, from 10 g. of oleic acid, after crystallisation from alcohol, 6·7 g., m. p. 44·5°.

All the monoglycerides were prepared by the methods given in Part II (*loc. cit.*, p. 1634).

α-Monoerucin. A mixture of 7·5 g. of *iso*propylidene glycerol and 5 g. of erucic acid was gently warmed to melt the acid, and dry hydrogen chloride passed through for ½ hour. After cooling, the cloudy liquid was transferred to a stoppered bottle, standing in ice, and washed in with about 25 c.c. of ether. 70 C.c. of well-cooled concentrated hydrochloric acid were then added gradually, with shaking, during one hour, after which 150 c.c. of ice-cold distilled water were added gradually, with shaking, during a further ½ hour. The monoerucin separated as a fine powder and was filtered off and well washed free from acid with water. In order to remove all traces of mineral acid before crystallisation it was taken up in ether, washed till neutral, dried over sodium sulphate, and after removal of the ether, crystallised from light petroleum (b. p. 40—60°); yield, 4·4 g., m. p. 50°.

α-Mono-olein, α-monoelaidin and α-monobrassidin. These glycerides were made as described for α-monodecoin in Part II, the only difference being that in the case of monobrassidin the hydrolysis of the intermediate compound takes a little longer (2—3 mins.). Yields of crystallised product from 5 g. of acid were: α-mono-olein, 3 g., m. p. 35°; α-monoelaidin and α-monobrassidin, 4 g., m. p.'s 58·5° and 71°, respectively.

All the monoglycerides crystallise well from light petroleum, hexane, and hexane–benzene.

αα′-Diglycerides. These were made by the action of the acid chloride on the α-monoglyceride, as described for αα′-dilaurin in Part III (p. 1412), the acid chlorides having been made by the action of oxalyl chloride on the acid (Adams and Uhlich, *J. Amer. Chem. Soc.*, 1920, **42**, 599). The main point in these preparations is to avoid formation of triglyceride, as this is removed from diglyceride only with great difficulty whereas α-monoglyceride is removed easily by crystallisation from alcohol: the α-monoglyceride should, therefore, be in slight excess. Yields of the order of 70% (on the acid chloride used) of crystallised material were obtained, except in the case of diolein, where crystallisation losses are high (1 g. from 3 g. of α-mono-olein). All crystallise well from hexane and hexane–benzene.

Triglycerides. These are made by the action of the acid chloride on the α-mono-compound as described for diglycerides, except that slight excess of the theoretical amount of acid chloride may be used, but the simplest method is to heat the α-monoglyceride with the theoretical amount of acid on the water-bath for one hour, in the presence of ½% of toluene-*p*-sulphonic acid, applying a vacuum from the water pump. Unchanged α-monoglyceride and acid are readily removed by crystallisation from alcohol, the final crystallisation being from alcohol for trierucin, and alcohol–benzene for trielaidin and tribrassidin; yields, 75—80%.

The following three glycerides are new: *α-monobrassidin* (Found: C, 73·0; H, 11·8. $C_{25}H_{48}O_4$ requires C, 72·8; H, 11·7%); *α-monoerucin* (Found: C, 72·8; H, 11·8. $C_{25}H_{48}O_4$ requires C, 72·8; H, 11·7%); *αα′-dielaidin* (Found: C, 75·3; H, 11·7. $C_{39}H_{72}O_5$ requires C, 75·5; H, 11·6%).

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THE UNIVERSITY, BRISTOL. [*Received, August 2nd*, 1946.]

NOTES.

Note on "Syntheses in the Indole Series. Part II." (*J.*, 1946, 461). By JOHN W. BAKER.

THE author's attention has been called to the fact that the reaction of acid chlorides of the type $CO_2R{\cdot}[CH_2]_n{\cdot}COCl$ ($n = 0$ or 1) (cf. also *J.*, 1940, 458) with indolylmagnesium iodide, described in the above communications, had previously been published by Oddo and Albanese (*Gazzetta*, 1927, **57**, 827), who actually prepared ethyl β-keto-β-3-indolylpropionate, identical in m. p. 121°, with the product obtained by the present author. It is regretted that the earlier publication was inadvertently overlooked, and acknowledgment is now made.—THE UNIVERSITY, LEEDS. [*Received, January 17th*, 1947.]

The Mechanism of Substitution at a Saturated Carbon Atom. By A. G. EVANS, M. G. EVANS, and M. POLANYI.

IN a recent paper by Dostrovsky, Hughes, and Ingold (*J.*, 1946, 173), calculations are made of the effect of steric hindrance on the activation energy of an organic substitution reaction. For the bimolecular reaction $X^- + R - X \longrightarrow X - R + X^-$ the transition state will involve resonance between two structures of equal energy, *viz.*, $X^-\ \ R - X$ and $X - R\ \ X^-$. Any such configuration is a possible transition state. To calculate the interatomic distances of the actual transition state one must find the configuration for which the potential energy is a minimum; the distances involved in the transition state are determined by this condition alone. The work of Polanyi (*Proc. Roy. Soc.*, 1934, *B*, **116**, 203), Ogg and Polanyi (*Trans. Faraday Soc.*, 1935, **31**, 604), and Baughan and Polanyi (*ibid.*, 1941, **37**, 648) has shown how this calculation can be made for symmetrical substitution reactions.

If the negative ion is assumed to be incompressible, then the minimum energy of the transition state is achieved when both the carbon–halogen distances are equal to the sum of the carbon radius and the ionic radius of X^-. This was used by Baughan and Polanyi as a first approximation in the determination of the transition-state configuration. There is no question here of determining the configuration of the transition state without considering the energy as a function of configuration. Steric compressions for the methyl to *tert.*-butyl halide series have been calculated by A. G. Evans and Polanyi (*Nature*, 1942, **149**, 608) using the transition-state distances obtained by Baughan and Polanyi.

Dostrovsky, Hughes, and Ingold (*loc. cit.*) claim to be able to define the configuration of the transition state by a different method. In the case of a symmetrical bimolecular reaction as discussed above they would obtain the transition-state distance by adding the covalent radius of carbon to the mean of the covalent and negative ionic radii of the halogen (p. 176). They point out that this procedure differs from that of Baughan and Polanyi, who take the full negative ionic radius of the halogens, and they suggest that their procedure is more correct since there is only one unit of charge shared between the incoming and outgoing halogen. This seems to indicate a misunderstanding of the approximation used by Baughan and Polanyi. We believe that any proper determination of transition-state distances, however approximate in nature, must necessarily involve a consideration of the dependence of energy upon these distances.

The authors do in fact use the method of Ogg and Polanyi at a later stage to calculate the absolute value of the activation energy. On this occasion they compare the transition-state distances obtained from their own method with those obtained from the correct application of the transition-state method, and a measure of agreement is found. Any such agreement, however, must be regarded as fortuitous.

An important point is the conclusion to be drawn about the existence of polar effects in the series methyl to *tert.*-butyl halides. These authors find that in this series the increase in activation energy calculated as due to steric hindrance is about one half of that found experimentally. They conclude from this that about one half of the increase in the bimolecular activation energy along this series is due to the induction effect. In our experience, the type of calculation involved here is not sufficiently exact to warrant such a quantitative conclusion. We feel, therefore, that for the primary to tertiary halide series there is no evidence that the decrease in the bimolecular reaction rate is due to anything other than the increase in steric repulsion energy along this series as postulated by Polanyi, Ogg, and A. G. Evans (*locc. cit.*), Meer and Polanyi (*Z. physikal. Chem.*, 1932, *B*, **19**, 164), and A. G. Evans (*Nature*, 1946, **157**, 438).—UNIVERSITY OF MANCHESTER. [*Received, July, 29th*, 1946.]

The Preparation and Properties of Thiol-esters. By CHARLES E. DALGLIESH and FREDERICK G. MANN.

Phenyl chlorothiolacetate, Ph·S·CO·CH_2Cl (I), is readily prepared in 95% yield by the action of chloroacetyl chloride on an ice-cold aqueous alkaline solution of thiophenol. The *p*-tolyl ester can be similarly prepared, and is identical with that obtained by Arndt and Bekir (*Ber.*, 1930, **63**, 2390) who proved its constitution. This method of preparation is similar to Chattaway's method (*J.*, 1931, 2495) of acetylating phenols in alkaline solution with acetic anhydride, and is of interest because it is generally stated (cf. " Organic Chemistry ", Gilman, 2nd Edtn., 1944, p. 932) that aliphatic acid chlorides are too readily hydrolysed to be used in aqueous suspension, and react with thiophenols and alkyl thiols only under anhydrous conditions.

Although ω-chloroacetanilide, Ph·NH·CO·CH_2Cl, can be readily cyclised to oxindole, and phenylthioacetyl chloride, Ph·S·CH_2·COCl, to thioindoxyl, (I) cannot be cyclised to thio-oxindole under similar conditions, probably because it enolises. This reaction, if it could be achieved, would be valuable, as Marschalk's preparation (*J. pr. Chem.*, 1913, **88**, 239) of thio-oxindole from oxindole is laborious and wasteful.

(I) reacts with *p*-toluidine to give thiophenol and chloroaceto-*p*-toluidide. It also reacts very readily with *p*-nitrosodimethylaniline to give diphenyl disulphide and 4 : 4′-bis(dimethylamino)azoxybenzene (II) :

$$2Ph\cdot S\cdot CO\cdot CH_2Cl + 2Me_2N\cdot C_6H_4\cdot NO + H_2O = Ph\cdot S\cdot S\cdot Ph + Me_2N\cdot C_6H_4\cdot N{:}N(\rightarrow O)\cdot C_6H_4\cdot NMe_2 + 2CH_2Cl\cdot CO_2H$$

(I.) (II.)

The azoxy-compound was also obtained when *p*-tolyl chlorothiolacetate was used, but not with phenyl thiolbenzoate, Ph·S·COPh. Several examples are known of the reaction of nitroso-derivatives with compounds containing the ·CO·CH_2X group (X = halogen) in the presence of pyridine (Krohnke and Borner, *Ber.*, 1936, **69**, 2006; Sanna, *Gazzetta*, 1942, **72**, 363); thus phenacyl bromide and nitrosobenzene give the nitrone, Ph·CO·CH:N(→O)·Ph. It is possible therefore that unstable intermediates of the nitrone type are formed in the course of the above reaction with *p*-nitrosodimethylaniline.

(I) reacts with thiourea to form 2-thiohydantoin, undoubtedly through the intermediate formation of *N*-chloroacetylthiourea.

Experimental.—Thiophenol (25 g.) was dissolved in a solution of sodium hydroxide (13·5 g., 1·5 mols.) in water (40 c.c.) containing crushed ice (150 g.). Chloroacetyl chloride (37 g., 1·5 mols.) was then rapidly added, and the whole vigorously shaken for 5 minutes. The solid *phenyl chlorothiolacetate* (I) (40 g., 95%) was collected, dried, and recrystallised from aqueous alcohol; colourless leaflets, m. p. 45° (Found : C, 51·7; H, 3·9; Cl, 19·5. C_8H_7OClS requires C, 51·5; H, 3·8; Cl, 19·0%).

A similar preparation, using thio-*p*-cresol (27·5 g.), afforded *p*-tolyl chlorothiolacetate (44 g., 98%), m. p. 40° after crystallisation from alcohol. Arndt and Bekir (*loc. cit.*) give m. p. 38°.

The similar use of benzoyl chloride afforded phenyl thiolbenzoate.

When (I) (1·9 g.) and *p*-toluidine (1·1 g., 1 mol.) were gently fused together, thiophenol was readily evolved. The cold residue, recrystallised from alcohol, furnished chloroaceto-*p*-toluidide (1·3 g., 70%), colourless needles, m. p. 161—162° (Found : N, 7·6. Calc. for $C_9H_{10}ONCl$: N, 7·6%).

A solution of *p*-nitrosodimethylaniline (9 g.) in alcohol (50 c.c.) was added to a solution of (I) (11·4 g.) in alcohol (40 c.c.), and the mixture boiled for 5 minutes and set aside (the reaction occurs, but more slowly, in the cold). The precipitated azoxy-compound (II) (5·5 g., 65%) was collected and recrystallised from benzene; glistening brown needles, m. p. 241° (Found : C, 67·7; H, 6·8. Calc. for $C_{16}H_{20}ON_4$:

C, 67·6; H, 7·0%. Consistent values for nitrogen could not be obtained). Previous workers have given m. p.'s ranging between 236° and 244°. The alcoholic filtrate was added to dilute hydrochloric acid (600 c.c.) and extracted with ether; evaporation of the dried extract gave diphenyl disulphide, (5·2 g.), colourless crystals from alcohol, m. p. 60° (Found: C, 66·0; H, 4·7; S, 29·4. Calc. for $C_{12}H_{10}S_2$: C, 66·1; H, 4·6; S, 29·4%).

(II) gave a *monopicrate* which separated from benzene as ruby-red needles, m. p. 144° (decomp.), containing benzene of crystallisation (Found: C, 54·8; H, 4·7; N, 18·0. $C_{16}H_{20}ON_4,C_6H_3O_7N_3,\frac{1}{2}C_6H_6$ requires C, 54·3; H, 4·7; N, 17·8%); heating at 80°/0·1 mm. for 3 hours gave yellow needles of the benzene-free picrate, m. p. unchanged (Found: C, 51·9; H, 4·7; N, 19·2. $C_{16}H_{20}ON_4,C_6H_3O_7N_3$ requires C, 51·5; H, 4·5; N, 19·1%). (II) gave a *distyphnate*, which crystallised from benzene as yellow needles, m. p. 148° (decomp.), which also contained benzene of crystallisation (Found: C, 46·1; H, 3·8; N, 17·4, 17·0. $C_{16}H_{20}ON_4,2C_6H_3O_8N_3,\frac{1}{2}C_6H_6$ requires C, 45·8; H, 3·6; N, 17·2%). (II) did not apparently form a methiodide.

The identity of (II) was further confirmed by reductive acetylation (cf. Dalgliesh and Mann, *J.*, 1945, 894). A mixture of (II) (3 g.), acetic acid (30 c.c.), acetic anhydride (30 c.c.), and zinc dust was refluxed for 3·5 hours and filtered; the residue was extracted with boiling acetic acid, and the combined filtrates were poured into water. After concentration and cooling, *p*-dimethylaminoacetanilide, $Me_2N{\cdot}C_6H_4{\cdot}NHAc$, white plates, m. p. 130°, was obtained (Found: N, 15·8. Calc. for $C_{10}H_{14}ON_2$: N, 16·0%). Further concentration gave successive crops of the same compound.

A mixture of (I) (5 g.), thiourea (2·05 g.), alcohol (25 c.c.), and water (5 c.c.) was refluxed for 2 hours, cooled, diluted with water, and basified. The solution deposited 2-thiohydantoin, white needles (1·25 g.), m. p. 228° (decomp.) after recrystallisation from aqueous alcohol. Wheeler, Nicolet, and Johnson (*Amer. Chem. J.*, 1911, **46**, 469) give m. p. 228°. It gave a *picrate*, yellow needles from alcohol, m. p. 195—198° (decomp.) (Found: N, 20·3. $C_3H_4ON_2S,C_6H_3O_7N_3$ requires N, 20·3%).

During preliminary experiments on the action of chloroacetyl chloride on sodium thiophenoxide suspended in organic liquids, one of the products isolated was *phenyl phenylthiothiolacetate*, $Ph{\cdot}S{\cdot}CO{\cdot}CH_2{\cdot}S{\cdot}Ph$, pale brown crystals from alcohol, m. p. 64—65° (Found: C, 64·0; H, 4·5. $C_{14}H_{12}OS_2$ requires C, 64·6; H, 4·6%).—University Chemical Laboratory, Cambridge. [*Received, August 17th*, 1946.]

4-p-*Aminostyryl-* and 2 : 6-*Di*-p-*aminostyryl-pyridine*. By Richard Royer.

A search of the literature reveals several cases of styrylpyridines where different authors have assigned the same constitution to two substances of widely-differing solubilities and melting points. In each case the analytical figures appear satisfactory, but the higher-melting substance has been prepared in a roundabout way. The present work provides the first direct syntheses of the higher-melting compounds, thus confirming their constitution. It is assumed that the problem is one of geometrical isomerism and that the lower-melting and more soluble forms are probably the *cis*-isomerides. However, repetition of the procedures described for producing the low-melting forms gave only the high-melting compounds.

4-p-*Nitrostyrylpyridine* (*4′-Nitro-4-stilbazole*.)—Baumert (*Ber.*, 1906, **39**, 2971) obtained the low-melting form (m. p. 118—119°) by heating 4-methylpyridine, *p*-nitrobenzaldehyde, and zinc chloride. By the nitration of 4-styrylpyridine, Wagstaff (*J.*, 1934, 276) obtained a substance of m. p. 171° (apparently corrected) to which he assigned this constitution as it gave a 24% yield of *p*-nitrobenzoic acid on oxidation with nitric acid (*d* 1·42). The following is the first direct synthesis of this compound.

4-Methylpyridine (1·9 g.; Eastman's pure), *p*-nitrobenzaldehyde (3·0 g.; 1 mol.), and acetic anhydride (2·0 g.; 1 mol.) were refluxed for 5 hours in a bath at 155—160°. Crystals separated on cooling and were filtered off, washed with acetic acid, then with water, and dried (4·1 g.; m. p. 150—153°). Recrystallisation from ethanol gave Wagstaff's 4-*p*-nitrostyrylpyridine (2·8 g.; 60%), m. p. 167—168° (170—171° corr.).

4-p-*Aminostyrylpyridine*. Baumert (*loc. cit.*) reduced his nitro-compound with stannous chloride and obtained a substance, m. p. 138—139°, readily soluble in ethanol, ether, and chloroform, and analysing for 4-*p*-aminostyrylpyridine. Wagstaff did not reduce his compound.

4-*p*-Nitrostyrylpyridine (2·0 g.; m. p. 167—168°) was added during ten minutes to a solution of hydrated stannous chloride (7·5 g.; 25% excess) in concentrated hydrochloric acid (8 ml.) maintained in a boiling water-bath. Heating was continued for 1½ hours with occasional stirring. The thin paste was poured into 2·5N-sodium hydroxide and excess of the latter added until Orange-II paper was reddened. The solid was filtered off, dried, and continuously extracted (Soxhlet) with acetone, giving 1·46 g. (85%) of yellow crystals, m. p. 273—274°. After repeated recrystallisation from ethanol and washing with acetone, the m. p. became steady at 275° (285° corr.). The substance consists of yellow crystals, slightly soluble in methanol, soluble in about 270 parts of boiling (and 600 parts of cold) ethanol and only slightly soluble in boiling benzene, chlorobenzene, chloroform, ether, or acetone (Found: C, 79·6; H, 6·2; N, 14·3%. $C_{13}H_{12}N_2$ requires C, 79·55; H, 6·2; N, 14·3%). It is evident that this is a form of 4-p-*aminostyrylpyridine*, higher-melting and less soluble than that described by Baumert, and that the two amino-compounds differ from one another in much the same way as the isomeric nitro-compounds from which they were derived.

Concentrated hydrochloric acid dissolves the high-melting base to give a faintly yellow solution which becomes quite colourless on dilution to N/2 acid and yellow on further dilution (N/20 acid), the latter being the colour of the freely soluble monohydrochloride. The pale yellow diazo-solution couples (crimson) with β-naphthol. The base dissolves with an orange colour in glacial (and a deep yellow colour in N-) acetic acid; the higher melting form of the similarly constituted 5-*p*-aminostyrylacridine is yellow and gives a violet solution in acetic acid (Sharp, Sutherland, and Wilson, *J.*, 1943, 5).

2 : 6-*Di*-p-*nitrostyrylpyridine*.—Werner (*Ber.*, 1903, **36**, 1687) obtained the low-melting form (m. p. 168—169°) by melting together 2 : 6-dimethylpyridine, *p*-nitrobenzaldehyde, and zinc chloride. By nitrating 2 : 6-distyryl-pyridine, Wagstaff (*loc. cit.*) obtained a compound, m. p. 258° (apparently

corrected), to which he assigned the same constitution on the grounds of the analytical figures and the production of *p*-nitrobenzoic acid in 83% yield on oxidation with nitric acid. The following is the first direct synthesis of this compound.

2 : 6-Dimethylpyridine (5·35 g.; b. p. 142°), *p*-nitrobenzaldehyde (10·6 g.; 2 mol.), and acetic anhydride (30 g.; 6 mol.) were refluxed for 10 hours. The yellow crystals which separated on cooling were filtered off, washed with acetic acid, then with water, and dried at 110°. The yield was 54%, m. p. 251—253°, but only 40% was obtained after 5 hours' refluxing. Repeated recrystallisations from pyridine and from chlorobenzene gave material of constant m. p. 253—254° (262—263° corr.) and agreeing with Wagstaff's description in all other respects. Identical results were obtained with two specimens of pure 2 : 6-dimethylpyridine, one of Australian and one of American origin.

2 : 6-*Di*-p-*aminostyrylpyridine*.—Werner (*loc. cit.*) reduced his nitro-compound with tin and hydrochloric acid and obtained a substance, m. p. 146°, readily soluble in dilute alcohol and analysing for 2 : 6-di-*p*-aminostyrylpyridine. Wagstaff did not reduce his compound.

2 : 6-Di-*p*-nitrostyrylpyridine (2·0 g.; m. p. 253—254°) was finely powdered, suspended in acetone (50 ml.), and reduced with hydrogen and Raney-nickel catalyst at atmospheric temperature and pressure until the calculated amount had been absorbed (2 hours). After filtration, the solution was concentrated to 20 ml. and treated with water (both liquids at 50°) until crystallisation began (0·72 g.; 44%; m. p. 230—231°). Repeated recrystallisation from dilute acetone raised the m. p. to 233°. The substance consists of golden crystals, sparingly soluble in boiling alcohol, benzene, and ether, moderately soluble in chlorobenzene and chloroform, and readily soluble in pyridine with green fluorescence (Found : C, 80·1; H, 6·1; N, 13·5. $C_{21}H_{19}N_3$ requires C, 80·5; H, 6·1; N, 13·4%). Obviously this is a higher-melting and less soluble 2 : 6-*di*-p-*aminostyrylpyridine* than that described by Werner.

The new substance does not evolve ammonia on boiling with 5N-sodium hydroxide. The hydrochloride is only sparingly soluble in water; the mono-acetate is deep orange and moderately soluble. The yellow diazo-solution couples (crimson) with β-naphthol.

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The Thermodynamic Properties of Isotopic Substances.

Liversidge Lecture, Delivered before the Chemical Society in the Royal Institution on December 18th, 1946.

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The discovery of the isotopes of the elements resulted from the careful study of the properties of radioactive substances during the first years of this century. The conclusion that certain species of atoms had identical chemical properties but different radioactive properties came from chemical studies which accompanied the study of radioactivity. Boltwood [1] noted that thorium and ionium were very similar in chemical properties, so similar, in fact, that he was unable to separate them if they were mixed. Marckwald and Keetman [2] investigated this problem with greater care, as did Auer v. Welsbach [3], and all these authors came to the conclusion that ionium and thorium are identical in chemical properties. Further, Marckwald [4] and Soddy [5] showed that radium and mesothorium constitute another such pair of substances. At present many such radio-elements which are chemically the same elements or are identical with non-radioactive elements are known. Soddy was able to conclude that this occurrence of two or more varieties of elements of identical chemical properties was probably of general occurrence, and that such identical elements differed in atomic weight as well as radioactive properties, and Sir J. J. Thompson proved that such isotopes existed in the case of stable atoms as well and detected them by the action of electric and magnetic fields on beams of ionized atoms which separated the atoms of different atomic weights. The outstanding work of Aston then gave us an extensive knowledge of the isotopes of the elements and their exact masses, and this has been followed by many researches which have completed or nearly completed our knowledge of this field.

Lindemann [6] first applied statistical mechanical methods to the problem of chemical differences of isotopes. He applied these calculations to the differences in vapour pressures of the lead isotopes and showed that considerable differences should exist if the half quantum of zero point energy were not present. Since experiments showed no difference in vapour pressure, he concluded that the half quantum of zero point energy must exist. Neither the method of calculation nor the conclusions have been changed by any work since this pioneer work of Lindemann, but it is unfortunate that this work was done on a heavy element, for all differences in chemical properties of isotopic compounds diminish rapidly with increasing atomic weight. Had these experiments been applied to water, using precision methods for determining density, positive results would have been secured.

Keesom and van Dijk [7] did demonstrate that differences in the vapour pressures of the neon isotopes exist by fractionally distilling liquid neon at $-$ 248·4°, and partially separated the neon isotopes in considerable quantity by this method. Urey, Brickwedde, and Murphy [8] showed that a large difference in the vapour pressures of the isotopic molecules of hydrogen, H_2 and HD, was to be expected even though the zero point energy was assumed, and concentrated the heavy isotope of hydrogen sufficiently to make its detection possible. Also, Lewis and Cornish [9] demonstrated the existence of vapour-pressure differences between the isotopic molecules, H_2O^{16}, D_2O^{16}, and H_2O^{18}. Urey and Rittenberg [10] showed from theoretical calculations that marked differences in the equilibrium constants of exchange reactions between hydrogen and deuterium on the one hand, and the hydrogen and deuterium compounds of the halogens on the other should exist, and Farkas and Farkas [11] applied the same methods to exchanges with water. Urey and Greiff [12] then applied the same methods to exchange reactions involving other isotopes. These researches first established the existence of comparatively large differences in properties of the hydrogen and deuterium compounds and of smaller but definite differences in the chemical properties of other isotopic compounds of elements of low atomic weight.

The marked differences in chemical properties of protium and deuterium and their compounds stimulated many researches on these substances during the 'thirties, and a very considerable literature on them exists at the present time. It is not the purpose of this paper to review this literature in detail, but rather to review a limited amount of this interesting work in relation to similar work on the isotopic compounds of other elements where the effects observed are much smaller. Also, the present paper is limited to equilibrium properties and does not include work dealing with differences related to the kinetics of chemical reactions. These latter effects

are largely unknown for isotopic compounds other than those of hydrogen except in so far as they relate to properties directly related by simple kinetic theory to molecular weights, as in the case of diffusion processes, or to molecular weights and forces between molecules, as in the case of the thermal diffusion method of separating isotopes, where the emphasis has largely been on the separation problem rather than on the fundamental properties of substances.

The theory of these differences in thermodynamic properties of isotopic compounds is well known in special cases and not in others. The physical properties of the elementary hydrogens, H_2, HD, and D_2, have been extensively studied [13] and the vapour pressure of protium tritide, HT, in its solution in natural hydrogen has been determined at one temperature.[14] The differences in vapour pressures are large and the heat capacity measurements on H_2, HD, and D_2 show that the Debye frequencies are so large that the heat capacities of the condensed phases are much less than those expected for high temperatures. This makes the differences in vapour pressures understandable in a qualitative way, though quantitative agreement is not secured since the Debye 0's are not inversely proportional to the molecular weights. Other attempts to correlate these properties have been made by Bijl and Hobbs [15] and better but not completely satisfactory agreement secured.

The differences in the vapour pressures of other compounds of protium and deuterium have been observed but no satisfactory theory with regard to these differences exists. With the exception of the hydrogens and the neons, none of these vapour pressure differences can be satisfactorily related to the translational or sound vibrations of the solids or liquids. The isotopic compounds of the hydrogens differ in heats of fusion, vaporisation, molar volumes, heats of solution and many other ways. These differences in the hydrogen compounds have prompted the study of similar differences between the isotopic compounds of other elements, and though the differences are very much smaller, they show similarities to the differences in the hydrogen compounds. These differences in the case of hydrogen as well as other of the lighter elements could not have been overlooked during the 19th century had there not been a sort of conspiracy in Nature which prevented their observation until other evidence indicated both the existence of isotopes and their chemical differences. Thus the hydrogen isotopes and their compounds are markedly different, but the extreme rarity of the heavy isotope prevented the observation of these differences. Similarly, carbon, nitrogen, and oxygen should show variations in their atomic weights, but the rarity of their isotopes makes observation difficult, though not at all impossible in the case of oxygen because of the great sensitivity with which the density of water may be determined. Variations in the properties of the compounds of lithium and boron are difficult to detect because of the general chemical character of their compounds, or failure to study them as quantitatively as the compounds of other elements have been covered. Only in the case of oxygen and chlorine should the variations of atomic weight have been noticed, and that they were overlooked in these cases was understandable in view of the size of the expected variations.

The Theory of the Equilibrium Constants of Exchange Reactions.

The differences in chemical properties of isotopic substances are mostly not exactly correlated in theoretical calculations with physical observations, but in the case of exchange reactions the observed phenomena are well correlated with the energy states of the molecules as secured from spectral data by the use of statistical mechanics. These correlations show the physical basis for the differences in these special cases, and throw light on the nature of other phenomena.

A typical exchange reaction may be written

$$aA_1 + bB_2 = aA_2 + bB_1$$

where A and B are molecules which have some one element as a common constituent and the subscripts 1 and 2 indicate that the molecule contains only the light or the heavy isotope respectively. (The case of molecules containing both isotopes simultaneously will be considered later.) Then the equilibrium constant for this reaction is given by

$$K = \left(\frac{Q'_{A_2}}{Q'_{A_1}}\right)^a \Big/ \left(\frac{Q'_{B_2}}{Q'_{B_1}}\right)^b \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where the Q's are the partition functions of the molecules. Only the ratios of partition functions enter into these equilibrium constants and this makes it necessary to consider only these simple ratios here.[16] The ratio Q'_2/Q'_1 for a chemical compound is given rigorously by the equation

$$\frac{Q'_2}{Q'_1} = \frac{\sigma_1}{\sigma_2}\left(\frac{M_2}{M_1}\right)^{3/2} \Sigma e^{-E_2/kT} / \Sigma e^{-E_1/kT} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where σ_2, and σ_2 are the symmetry numbers of the two molecules (identical in the example given), M_1 and M_2 are their molecular weights, E_1 and E_2 are particular energy states of the molecules, and the summations are to be taken over all such energy states. These energies must be calculated relative to the hypothetical vibrationless state, *i.e.*, with no zero point energy, or relative to the completely dissociated molecules. Since it is not possible to determine the energies of isotopic molecules relative to the dissociated states, and since the zero point energies cannot be directly observed, it is necessary to assume that the potential functions are the same for isotopic molecules, and estimate the zero point energies from the empirical but theoretically justified formulæ of molecular energy levels. If the temperature is so high that kT is large compared with the separations of the rotational energy levels, as it is in most of the cases we shall consider, and if the vibrational energy levels are sufficiently nearly harmonic, equation (2) can be replaced by

$$\frac{Q'_2}{Q'_1} = \frac{\sigma_1}{\sigma_2}\frac{I_2}{I_1}\left(\frac{M_2}{M_1}\right)^{3/2}\frac{e^{-u_2/2}}{1-e^{-u_2}}\frac{1-e^{-u_1}}{e^{-u_1/2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

for diatomic molecules and

$$\frac{Q'_2}{Q'_1} = \frac{\sigma_1}{\sigma_2}\left(\frac{A_2B_2C_2}{A_1B_1C_1}\right)^{1/2}\left(\frac{M_2}{M_1}\right)^{3/2}\Pi_i\frac{e^{-u_{2i}/2}}{1-e^{-u_{2i}}}\frac{1-e^{-u_{1i}}}{e^{-u_{1i}/2}} \quad . \quad . \quad . \quad . \quad (4)$$

for polyatomic molecules where the I's and A's, B's, and C's are the moments of inertia of the diatomic molecules and the principle moments of inertia of the polyatomic molecules, respectively, and the u's are related to the corresponding frequencies of vibration by relations of the kind, $u_i = hc\omega_i/kT$, and the product extends over all frequencies of the polyatomic molecule. If the right and left sides of equations (3) and (4) are multiplied by $(m_1/m_2)^{3/2n}$, where m_1 and m_2 are the atomic weights of the isotopic atoms being considered and n is the number of isotopic atoms being exchanged, and if the right sides of (3) and (4) are multiplied and divided by the ratios u_1/u_2 and $\Pi_i\, u_{1i}/u_{2i}$ respectively, it is possible to simplify these expressions and define new partition functions which are in fact the equilibrium constants for exchange reactions between the compound considered and the separated atoms. Thus (3) and (4) became

$$\frac{Q_2}{Q_1} = \frac{\sigma_1}{\sigma_2}\frac{u_2}{u_1}\frac{e^{-u_2/2}}{1-e^{-u_2}}\frac{1-e^{-u_1}}{e^{-u_1/2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3')$$

and

$$\frac{Q_2}{Q_1} = \frac{\sigma_1}{\sigma_2}\Pi_i\frac{u_{2i}}{u_{1i}}\frac{e^{-u_{2i}/2}}{1-e^{-u_{2i}}}\frac{1-e^{-u_{1i}}}{e^{-u_{1i}/2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4')$$

since

$$\frac{I_2}{I_1}\left(\frac{M_2}{M_1}\right)^{3/2}\left(\frac{m_1}{m_2}\right)^{3/2n}\frac{u_1}{u_2} = \left(\frac{A_2B_2C_2}{A_1B_1C_1}\right)^{1/2}\left(\frac{M_2}{M_1}\right)^{3/2}\left(\frac{m_1}{m_2}\right)^{3/2n}\Pi_i\frac{u_{1i}}{u_{2i}} = 1$$

according to a theorem of Teller and Redlich.[17] This makes it possible to calculate these ratios without calculating the moments of inertia and, in fact, from a knowledge of the frequencies only. Of course, it is necessary to secure the frequencies for isotopic molecules either by direct observation or by calculation in the case of rarer isotopes, and in this latter case much information is often needed in order to make the necessary calculations. It is obvious that the equilibrium constant K is given by

$$\left(\frac{Q_{2A}}{Q_{1A}}\right)^a \Big/ \left(\frac{Q_{2B}}{Q_{1A}}\right)^b = K$$

for the general exchange reaction just as it is given by (1).

The equations (3′) and (4′) can be put into more convenient form for purposes of calculation. Defining

$$x_i = \frac{u_{1i}+u_{2i}}{4} \quad \text{and} \quad \delta_i = \frac{u_{1i}-u_{2i}}{2} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

and expanding in terms of the δ_i's, we get [18]

$$\ln\frac{Q_2}{Q_1} = \ln\frac{\sigma_1}{\sigma_2} + \Sigma_i \ln\frac{u_{2i}}{u_{1i}} + \Sigma_i[\coth x_i\delta_i + \frac{1}{12}\coth x_i\,(\coth^2 x_i - 1)\,\delta_i^3 + - - -] \; . \quad (6)$$

This equation can be used without the term in δ_i^3 for all calculations reported in this paper except those of LiH, LiD; NaH, NaD; KH, KD; and H_2O, D_2O.

If the u's are small, *i.e.*, either the frequencies low or the temperature high, the right sides of equations (3′) and (4′) can be easily expanded to give

$$\frac{Q_2}{Q_1} = \frac{\sigma_1}{\sigma_2}\left(1 - \frac{1}{24}(u_2^2 - u_1^2)\right) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

and

$$\frac{Q_2}{Q_1} = \frac{\sigma_1}{\sigma_2}\pi_i\left[1 - \frac{1}{24}(u_{2i}^2 - u_{1i}^2)\right] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Since the u's contain the inverse of the temperature, the ratio of the Q's approaches the ratio of the symmetry numbers, and in this case no differences in chemical properties exist. The partition function ratio Q'_2/Q'_1 approaches the value $\frac{\sigma_1}{\sigma_2}\left(\frac{m_2}{m_1}\right)^{3/2}$ instead of $\frac{\sigma_1}{\sigma_2}$ in the case of Q_2/Q_1.

Bigeleisen and Mayer have shown how this formula can be used without solving the equations of motion, and have applied these methods to the silicon and tin fluorides and the fluorosilicate and fluorostannate ions.

For precise calculations it is necessary to include the anharmonic terms in the vibrational energy. When the frequencies are small these terms may be neglected and when they are large coth x_i is nearly equal to unity. In the case of diatomic molecules a correction for the anharmonicity terms can be made by substituting the true difference in zero point energies in calculating δ [equation (5)] instead of using harmonic terms only. In the case of polyatomic molecules this cannot be done since the anharmonic terms are not uniquely related to the ω_i's, because of cross product terms. In this case a sufficiently good approximation can be made by adding to equation (6) a term $\Delta E'/kT$, where $\Delta E'$ is the contribution to the zero point energy difference from the anharmonic energy terms. If the coefficients of the anharmonic terms are negative (the usual case) $\Delta E'$ is negative and decreases the calculated value of Q_2/Q_1.

Equations (3) and (4), (3′) and (4′) and (6) must be further corrected when the rotational partition functions have not reached classical values. Such corrections can be neglected at the temperatures which we consider here in all cases except those of the hydrogen exchange reactions. The formulæ for these corrections were first derived by Mulholland,[19] Viney,[20] and Gordon [21] and are reviewed in detail by Kassel.[22] The formulæ for these corrections are given for all cases by the last author.

If the molecule of a chemical compound under consideration contains only one atom of the element for which exchange is considered, then the symmetry numbers of the two isotopic molecules are the same and σ_1/σ_2 is equal to unity. Also if a molecule contains more than one such atom but these atoms occupy indistinguishable positions in the molecule and if they are all exchanged in the reaction considered, the ratio of symmetry numbers is again unity. When these conditions are not met, the ratio of symmetry numbers is not unity and their values must be determined for each particular case.

In general, we are interested in the overall ratio of the isotopes of an element in one chemical compound as compared with a similar ratio in a second chemical compound. Thus the fractionation of the isotopes of oxygen between carbon dioxide and water is given by the ratio

$$\frac{2[CO_2^{18}] + [CO^{16}O^{18}]}{[CO^{16}O^{18}] + 2[CO_2^{16}]} \Big/ \frac{[H_2O^{18}]}{[H_2O^{16}]} = \alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

It can easily be shown that this reduces to

$$\frac{[CO_2^{18}]^{1/2}}{[CO_2^{16}]^{1/2}} \Big/ \frac{[H_2O^{18}]}{[H_2O^{16}]} = \alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

if the equilibrium constant for the reaction

$$CO_2^{18} + CO_2^{16} = 2\ CO^{16}O^{18}$$

is 4, and this will be true providing the partition function for the molecule $CO^{16}O^{18}$ is the geometric mean of those for CO_2^{16} and CO_2^{18} divided by their symmetry numbers so that the equilibrium constant is $\sigma_1\sigma_2/\sigma_{12}^2$, and since σ_1 and σ_2 are 2 and σ_{12} is 1, this equals 4. Similarly, the fractionation factor for the distribution of the oxygen isotopes between CO_2 and $CO_2^{=}$ will be

$$\frac{[CO_2^{18=}]^{1/3}}{[CO_2^{16=}]^{1/3}} \Big/ \frac{[CO_2^{18}]^{1/2}}{[CO_2^{16}]^{1/2}}$$

if the proportion of the isotopic molecules is determined by the symmetry numbers alone. The generalisation of this rule is obvious, but it will not apply to molecules in which two or more

atoms of the same element do not occupy equivalent positions, as for example the case of nitrogen in the unsymmetrical molecule, N_2O. Also this rule does not apply in the case of the hydrogen isotopes where the isotopic effect on vibration frequencies is very large.

The justification of the rules given in the preceding paragraph is difficult unless one calculates the vibration frequencies of all the molecules involved, and this is a very laborious task which has not been extensively undertaken. In the case of the exchange between CO_2^{16}, CO_2^{18}, and $CO^{16}O^{18}$, the equilibrium constant has been calculated [23] and found to be 3·9990 at 0°. α is decreased by $\left(1-\frac{\Delta}{8}\right)$ at low concentrations of the heavy isotope and increased by $\left(1+\frac{\Delta}{8}\right)$ at high concentrations of this isotope, where Δ is the difference between 4 and the actual constant. The equilibrium constants for the exchange between O_2^{16}, O_2^{18}, and $O^{16}O^{18}$ and N_2^{14}, N_2^{15}, and $N^{14}N^{15}$ are 3·9859 and 3·9918 respectively and the α's for reactions involving CO_2, O_2, and N_2 differ from those given by (6) by 1·000125, 1·0018, and 1·0010 respectively, all at 0° C. Errors of the same order of magnitude are probable in other cases. These are the largest deviations to be expected and are not important as compared to other probable errors. The special problem presented by the hydrogen isotopes will be considered again.

There is an electronic isotope effect for the H and D atoms of 30 cm.$^{-1}$, and isotope effects of this order of magnitude should be present for all compounds of protium and deuterium. It is improbable that they will always cancel completely, and since they are unknown, there are uncertainties in the calculations of the Q_2/Q_1 values for the protium and deuterium compounds. These uncertainties are greater in the case of the tritium compounds.

In the case of all polyatomic molecules except CO_2 and HCN and all ionic molecules only the observed fundamentals are known. In these cases the errors may be larger than estimated above because of errors in the calculation of the zero point energy, since anharmonic terms are unknown and because of errors in calculating the fundamentals of the rare isotopic mosecules from the observed fundamentals of the more abundant isotopic molecules. If the anharmonic terms are negative (the usual case) the neglect of this factor makes the calculated Q_2/Q_1 too small. In the case of CO_2 and HCN, positive and negative anharmonic terms occur and the total effect on the calculated ratio is small. We have no way of estimating the magnitude or even the sign of these uncertainties.

If equilibrium constants for exchanges between gaseous substances and substances in condensed phases are desired, calculations for such constants are readily made from the equilibrium constants for gaseous substances and the appropriate relative vapour pressures if they are known. Since ionic substances are always in solution or in a solid phase, it is to be expected that calculated constants neglecting such effects may be in error by as much as a factor of 1·01. Such differences must be due to the application of statistical mechanical formulæ applicable to ideal gaseous substances to condensed phases without considering the effects of interaction between internal vibrations of a molecule and the fields produced by the other molecules of the condensed phase.

In a number of cases equilibrium constants for exchange reactions change with temperature from a region in which K is greater than unity to one in which it is less than unity, or the reverse. This is not a general phenomenon but neither is it uncommon. By expanding $\ln u_{2i}/u_{1i}$ in equation (6) and neglecting the δ_i^3 terms, it is easy to show that in the region of large values for all u_i's

$$\ln K = \ln\left(\frac{f_{2A}}{f_{1A}}\right)^a \Big/ \left(\frac{f_{2B}}{f_{1B}}\right)^b = -a\Sigma\frac{\delta\omega_{iA}}{\omega_{iA}} + a\Sigma\delta_{iA} + b\Sigma\frac{\delta\omega_{iB}}{\omega_{iB}} - b\Sigma\delta_{iB}$$

or if $K = 1$ and we substitute the values of the δ_i's in terms of the $\delta\omega_i$'s and solve for T, we get

$$T_1 = \frac{a\Sigma\delta\omega_{iA} - b\Sigma\delta\omega_{iB}}{a\Sigma\left(\frac{\delta\omega}{\omega}\right)_{iA} - b\Sigma\left(\frac{\delta\omega}{\omega}\right)_{iB}} \cdot \frac{hc}{2k} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

for the temperature at which K crosses the value unity as the temperature increases. Applying the equation to some of these exchange reactions, we get the results shown in Table I. These

TABLE I.

Reaction.	$T(K=1)$.
$\frac{1}{2}H_2 + DI = \frac{1}{2}D_2 + HI$	114°
$D_2O^{16} + \frac{1}{2}O_2^{18} = D_2O^{18} + \frac{1}{2}O_2^{16}$	123
$H_2O^{16} + \frac{1}{2}O_2^{18} = H_2O^{18} + \frac{1}{2}O_2^{16}$	495
$CO^{16} + \frac{1}{2}CO_2^{18} = CO^{18} + \frac{1}{2}CO_2^{16}$	384

calculations are only approximate, since they neglect anharmonic effects and disagree in some cases with the more exact calculations of the other tables. This crossing will occur if the difference in the sums of differences of frequencies has the same sign as the differences in the sums of the fractional differences of frequencies.

Numerical Results.

The vibration frequencies available for such calculations are very numerous but vary considerably in reliability for these purposes. Table II contains a list of the frequencies of diatomic and polyatomic molecules used for the calculations presented here. Unless the anharmonic terms in the vibrational energy level formulæ are known, exact equilibrium constants

TABLE II.

Molecular Frequencies.

(a) *Diatomic molecules for which exact constants are known.*

Molecule.	ω_0.	$-x_0\omega_0$.	Ref. (see p. 568).	Molecule.	ω_0.	$-x_0\omega_0$.	Ref. (see p. 568).
HCl^{35}	2988·95	51·65	Herzberg, I, p. 488	NaH	1170·8	18·90	Herzberg, I, p. 490
DCl^{35}	2143·52	26·56	Calculated	NaD	845·3	9·84	Calculated
HCl^{37}	2987·5	51·57	Calculated	KH	983·3	14·40	Herzberg, I, p. 489
HBr^{79}	2649·67	45·21	Herzberg, I, p. 487	KD	704·2	7·38	Calculated
DBr^{79}	1885·95	22·90	Calculated	$C^{13}O^{16}$	2167·4	13·28	Herzberg, I, p. 486
HBr^{81}	2646·6	45·19	Calculated	$C^{13}O^{16}$	2119·2	12·69	Calculated
HI	2309·53	39·73	Herzberg, I, p. 488	CO^{18}	2115·2	12·65	Calculated
DI	1639·45	20·02	Calculated	N_2^{14}	2359·6	14·45	Herzberg, I, p. 490
H_2	4405·3	125·32	Herzberg, I, p. 487	N_2^{15}	2279·6	13·48	Calculated
HD	3817·09	94·02	Libby	$N^{14}O$	1906·54	14·50	Herzberg, I, p. 490
D_2	3118·8 }	64·15 }	Herzberg, I, p. 487	$N^{15}O$	1872·34	13·99	Calculated
	3117·07 }	62·72 }	Libby	O_2^{16}	1580·4	12·07	Herzberg, I, p. 490
HT	3598·14	83·60	Libby	O_2^{18}	1490·0	10·73	Calculated
DT	2845·64	52·28	Libby	Cl_2^{35}	564·9	4·0	Herzberg, I, p. 485
T_2	2546·50	41·88	Libby	Cl_2^{37}	549·4	3·8	Calculated
Li^6H	1420·32	23·69	Calculated	Br_2^{79}	323·86	1·07	Herzberg, I, p. 484
Li^6D	1074·59	13·72	Calculated	Br_2^{81}	319·84	1·04	Calculated
Li^7H	1405·65	23·20	Herzberg, I, p. 489	I_2^{127}	214·36	0·59	Herzberg, I, p. 488
Li^7D	1055·12	13·23	Herzberg, I, p. 489	I_2^{129}	212·69	0·58	Calculated

(b) *Diatomic molecules for which only the frequencies for the observed fundamentals are known.*

$C^{13}N^{14}-$	2080	Estimated from Hibben, p. 453	$C^{13}N^{14}-$	2036·47	Calculated
			$C^{13}N^{15}-$	2047·76	Calculated

(c) *Polyatomic molecules for which exact constants are known. The multiplicity of degenerate frequencies is indicated in parentheses.*

Molecules.	ω_1.	x_{ij}.			Ref. (see p. 568).	Molecules.	ω_1.	x_{ij}.			Ref. (see p. 568).
H_2O	3825·32	−43·89	−	20·02	Herzberg,	D_2O^{16}	2744·2	−22·58	−	10·44	Calc., Val-
	1653·91	−19·5	−	155·06	II, p. 282		1202·7	−10·31	−	80·88	ence forces
	3935·59	−46·37	−	19·81			2861·7	−24·52	−	10·47	
HDO	2820·3	−42·27	−	89·3	Libby	CO_2	1351·20	− 0·3	+	5·7	Herzberg,
	1449·4	4·1	−	16·0			672·20(2)	− 1·3	−	21·9	II, p. 276
	3883·8	−77·39	−	25·53			2396·40	−12·5	−	11·0	
D_2O	2758·06	−22·81	−	10·56	Herzberg,	$C^{13}O_2$	1351·20	− 0·30	+	5·54	Calc., Val-
	1210·25	−10·44	−	81·92	II, p. 282		653·12(2)	− 1·23	−	21·28	ence forces
	2883·79	−24·90	−	10·62			2328·40	−11·80	−	10·38	
HTO	2365·0	−29·43	−	18·93	Libby	CO_2^{18}	1273·92	− 0·27	+	5·29	Calc., Val-
	1374·5	− 5·91	−	11·63			661·94(2)	− 1·26	−	20·33	ence forces
	3882·6	−77·70	−	26·95			2359·81	−12·12	−	10·67	
DTO	2357·1	−27·84	−	13·53	Libby	HCN	2000·6	+52·0	−	4·2	Herzberg,
	1117·9	−13·7	−	9·01			729·3(2)	− 2·85	−	14·40	II, p. 280
	2830·7	−41·77	−	11·3			3451·5	−55·48	−	19·53	
T_2O	2296·63	−15·71	−	4·27	Libby	$HC^{13}N$	1966·63	+50·25	−	4·09	Calc., Val-
	1017·89	− 8·21	−	56·79			722·96(2)	− 2·80	−	14·09	ence forces
	2436·12	−18·39	−	6·21			3435·38	−54·96	−	19·27	
H_2O^{18}	3815·5	−43·66	−	19·89	Calc., val-	HCN^{15}	1968·63	+50·36	−	4·13	Calc., Val-
	1647·8	−19·36	−	154·03	ence forces		728·22 (2)	− 2·84	−	14·17	ence forces
	3919·4	−45·99	−	19·66			3450·86	−55·46	−	19·50	

The frequencies are listed in the order ω_1, ω_2, and ω_3 and the x_{ij}'s in the order

$$\begin{matrix} x_{11} & x_{12} \\ x_{22} & x_{13} \\ x_{33} & x_{23} \end{matrix}$$

TABLE II.—*continued.*

Molecular Frequencies.

(d) *Polyatomic molecules for which only frequencies for the observed fundamentals are known.*

Molecule.	Frequencies.				Ref. (see below).
$B^{10}F_3$	888	719·5	1497(2)	482(2)	Anderson, Lassettre, and Yost
$B^{11}F_3$	888	691·3	1445·9(2)	480·4(2)	
$B^{10}Cl_3$ (l.)	471	471·5	989(2)	253(2)	
$B^{11}Cl_3$ (l.)	471	451	946(2)	253(2)	
$B^{10}Cl_3$ (g.)	471	483	996(2)	243(2)	
$B^{11}Cl_3$ (g.)	471	462	958(2)	243(2)	
$B^{10}Br_3$ (l.)	279	390	846(2)	151(2)	
$B^{11}Br_3$ (l.)	279	371·5	806(2)	151(2)	
$CO_3^=$	1087	878	1437(2)	714(2)	Urey and Greiff
$C^{13}O_3^=$	1087	850·56	1393·89(2)	712·81(2)	Calculated
$CO_3^{18}=$	1024·83	868·19	1415·87(2)	673·75(2)	Calculated, Hibben, p. 466
NH_4^+	3040	1725(2)	3142(3)	1411(3)	
$N^{15}H_4^+$	3040	1725(2)	3130·3(3)	1405·7(3)	Calculated, Rosenthal Herzberg, II, p. 164
NH_3	3337	950	3414(2)	1628(2)	
$N^{15}H_3$	3333·9	945·2	3403·9(2)	1625·1(2)	Calculated, Valence forces
$SO_4^=$	980	451·0(2)	1113·6(3)	618·9(3)	Urey and Greiff
$SO_4^{18}=$	924·0	425·2(2)	1081·9(3)	589·4(3)	Urey and Greiff
SO_2	1151	519	1361	—	Herzberg, II, p. 285
SO_2^{18}	1101·36	496·96	1317·07	—	Calculated
ClO_2	954	529	1105	—	Urey and Greiff
ClO_2^{18}	925·13	499·16	1070·18	—	Calculated, Valence forces
$Cl^{37}O_2$	949·29	524·72	1091·73	—	
ClO_4^-	935	462(2)	1102(3)	628(3)	Herzberg, II, p. 167
$Cl^{37}O_4^-$	935	462(2)	1085·31(3)	626·42(3)	Calculated, Valence forces
ClO_3^-	932	615	980(2)	480(2)	Kujemzelis
$Cl^{37}O_3^-$	917·80	614·67	971·20(2)	479·14(2)	Calculated, Valence forces
$Br^{79}O_3^-$	805	420	810(2)	358(2)	Kujemzelis
$Br^{81}O_3^-$	802·91	419·12	808·31(2)	357·75(2)	Calculated, Valence forces
$I^{127}O_3^-$	798	365	780(2)	323(2)	Kujemzelis
$I^{129}O_3^-$	797·20	364·58	779·33(2)	322·89(2)	Calculated, Valence forces

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TABLE III.

*Ratios of Partition Functions for Hydrogen and Water Molecules.**

Molecule pair.	Temp. ° K.				
	273·1	298·1	400.	500.	600.
HD/H_2	7·6282	6·7366	4·7672	3·8941	3·4030
D_2/HD	2·4017	2·0704	1·3715	1·0752	0·9154
$(D_2/H_2)^{\frac{1}{2}}$	4·2803	3·7346	2·5570	2·0462	1·7650
HT/H_2	12·496	10·537	6·5542	4·9642	4·1258
T_2/HT	5·1548	4·1182	2·2041	1·5298	1·2003
$(T_2/H_2)^{\frac{1}{2}}$	8·0260	6·5873	3·8008	2·7558	2·2254
DT/D_2	3·6482	3·4426	2·9246	2·6652	2·5034
T^2/DT	0·9617	0·9020	0·7545	0·6799	0·6346
$(T^2/D_2)^{\frac{1}{2}}$	1·8731	1·7622	1·4855	1·3462	1·2605
HDO/H_2O	32·7400	24·9460	11·7240	7·5602	5·6614
D_2O/HDO	8·3185	6·3065	2·9282	1·8791	1·4044
$(D_2O/H_2O)^{\frac{1}{2}}$	16·503	12·543	5·8592	3·7689	2·8196
HTO/H_2O	95·507	65·266	22·681	12·281	8·2027
T_2O/HTO	28·575	19·085	6·2523	3·2871	2·1593
$(T_2O/H_2O)^{\frac{1}{2}}$	52·241	35·293	11·908	6·3535	4·1603
DTO/D_2O	5·9628	5·3294	3·9068	3·2674	2·9088
T_2O/DTO	1·6805	1·4857	1·0573	0·8696	0·7658
$(T_2O/D_2O)^{\frac{1}{2}}$	3·1656	2·8138	2·0324	1·6857	1·4925

* Rotation corrections were not made for any of the values for water listed in this table because the rotation constants for the mixed molecules are now known, and better values of the ratios are obtained if no corrections are made than if they are made for only some of the molecules.

TABLE IV.

Equilibrium Constants for Hydrogen and Water Exchange.

Equilibrium.	Temp., ° K. 0.	273·1.	298·1.	400.	500.	600.
$[HD]^2/[H_2][D_2]$	0	3·18	3·25	3·48	3·62	3·72
$[HDO]^2/[H_2O][D_2O]$	0	3·94	3·96	4·00	4·02	4·03
$[HDO][H_2]/[H_2O][HD]$	∞	4·29	3·70	2·46	1·94	1·66
$[D_2O][HD]/[HDO][D_2]$	∞	3·46	3·05	2·14	1·75	1·53
$[HT]^2/[H_2][T_2]$	0	2·42	2·56	2·97	3·24	3·44
$[HTO]^2/[H_2O][T_2O]$	0	3·34	3·42	3·63	3·74	3·80
$[HTO][H_2]/[H_2O][HT]$	∞	7·64	6·19	3·46	2·47	1·99
$[T_2O][HT]/[HTO][T_2]$	∞	5·54	4·63	2·84	2·15	1·80
$[DT]^2/[D_2][T_2]$	0	3·79	3·82	3·88	3·92	3·94
$[DTO]^2/[D_2O][T_2O]$	0	3·55	3·59	3·70	3·76	3·80
$[DTO][D_2]/[D_2O][DT]$	∞	1·63	1·55	1·34	1·23	1·16
$[T_2O][DT]/[DTO][T_2]$	∞	1·75	1·65	1·40	1·28	1·21

TABLE V.

Hydrogen Exchange.

	$\left(\frac{D_2O}{H_2O}\right)^{\frac{1}{2}}$.	DCl/HCl.	DBr/HBr.	$\left(\frac{D_2}{H_2}\right)^{\frac{1}{2}}$.	DI/HI.	LiD/LiH.	NaD/NaH.	KD/KH.	T, ° K.
Q_2	16·467	6·3726	5·1278	4·2803	4·0172	1·8604	1·6908	1·5047	273·1
Q_1	12·518	5·3059	4·3454	3·7346	3·4744	1·7287	1·5819	1·4248	298·1
	5·8504	3·1881	2·7445	2·5570	2·3236	1·4151	1·3271	1·2377	400
	3·7648	2·3695	2·1013	2·0462	1·8434	1·2700	1·2105	1·1524	500
	2·8222	1·9493	1·7652	1·7650	1·5873	1·1891	1·1463	1·1055	600
		∞	∞	∞	∞	∞	∞	∞	0
$\left(\frac{D_2O}{H_2O}\right)^{\frac{1}{2}}$	1·000	2·584	3·211	3·847	4·099	8·851	9·739	10·944	273·1
		2·359	2·881	3·352	3·603	7·241	7·913	8·786	298·1
		1·835	2·132	2·288	2·518	4·134	4·408	4·727	400
		1·589	1·792	1·840	2·042	2·964	3·110	3·267	500
		1·448	1·599	1·599	1·778	2·373	2·462	2·533	600
			∞	∞	∞	∞	∞	∞	0
DCl/HCl		1·000	1·243	1·489	1·586	3·425	3·769	4·235	273·1
			1·221	1·421	1·527	3·069	3·354	3·724	298·1
			1·162	1·247	1·372	2·253	2·403	2·576	400
			1·128	1·158	1·285	1·866	1·957	2·056	500
			1·104	1·104	1·228	1·639	1·701	1·763	600
				∞	∞	∞	∞	∞	0
DBr/HBr			1·000	1·198	1·276	2·766	3·033	3·408	273·1
				1·164	1·251	2·514	2·747	3·050	298·1
				1·073	1·181	1·939	2·068	2·217	400
				1·027	1·140	1·655	1·736	1·823	500
				1·000	1·112	1·484	1·540	1·597	600
					0	∞	∞	∞	0
$\left(\frac{D_2}{H_2}\right)^{\frac{1}{2}}$				1·000	1·065	2·301	2·532	2·845	273·1
					1·075	2·160	2·361	2·621	298·1
					1·100	1·807	1·927	2·066	400
					1·110	1·611	1·690	1·776	500
					1·112	1·484	1·540	1·597	600
						∞	∞	∞	0
DI/HI					1·000	2·159	2·376	2·670	273·1
						2·010	2·196	2·439	298·1
						1·642	1·751	1·877	400
						1·451	1·523	1·600	500
						1·335	1·385	1·436	600
							∞	∞	0
LiD/LiH						1·000	1·100	1·236	273·1
							1·093	1·213	298·
							1·066	1·143	400
							1·049	1·102	500
							1·038	1·076	600
								∞	0
NaD/NaH							1·000	1·124	273·1
								1·110	298·1
								1·072	400
								1·050	500
								1·038	600

cannot be calculated. For this reason such compounds as H_2CO, H_2S, H_2Se, H_2O_2, and C_2H_2 have not been included although calculations of such constants have been reported in the literature.

In Table II the substances are classified into two groups, those for which the spectroscopic data are very reliable and detailed, and those for which only more approximate data are known. The equilibrium constants which depend on this second class of data are less reliable than those which depend on the first class only. Formulæ used for the calculations of frequencies of the rarer and unobserved isotopic molecule can be made by well-known methods for diatomic molecules, but a choice of formula must be made in the case of polyatomic molecules. Footnotes to the table indicate the type of formula used in these calculations.

In Tables III—XIII are recorded the values of the ratios of partition functions and equilibrium constants for exchange reactions involving the isotopes of H, Li, B, C, N, O, Cl, Br, and I. At the top under a symbol for the substance are given the values for Q_2/Q_1, at five temperatures, and then the equilibrium constants for all possible exchanges between these substances with respect to a particular isotope. A value in the body of the table is the

TABLE VI.

Lithium Exchange.

	$\frac{Li^7D}{Li^6D}$	$\frac{Li^7H}{Li^6H}$	$\frac{Li^7}{Li^6}$	T, ° K.
$\frac{Q_2}{Q_1}$	1·0334	1·0281	1·0000	273·1
	1·0292	1·0249	1·0000	298·1
	1·0181	1·0161	1·0000	400
	1·0123	1·0113	1·0000	500
	1·0089	1·0083	1·0000	600
		∞	∞	0
$\frac{Li^7D}{Li^6D}$	1·000	1·005	1·033	273·1
		1·004	1·029	298·1
		1·002	1·018	400
		1·001	1·012	500
		1·000$_5$	1·009	600
			∞	0
$\frac{Li^7H}{Li^6H}$		1·000	1·028	273·1
			1·025	298·1
			1·016	400
			1·011	500
			1·008	600

TABLE VII.

Boron Exchange.

	$\frac{B^{11}F_3}{B^{10}F_3}$	$\frac{B^{11}Cl_3\ (l.)}{B^{10}Cl_3\ (l.)}$	$\frac{B^{11}Cl_3\ (g.)}{B^{10}Cl_3\ (g.)}$	$\frac{B^{11}Br_3\ (l.)}{B^{10}Br_3\ (l.)}$	T, ° K.
$\frac{Q_2}{Q_1}$	1·2727	1·1739	1·1567	1·1441	273·1
	1·2374	1·1497	1·1350	1·1234	298·1
	1·1471	1·0891	1·0805	1·0724	400
	1·1005	1·0591	1·0536	1·0477	500
	1·0728	1·0420	1·0380	1·0336	600
		∞	∞	∞	0
$\frac{B^{11}F_3}{B^{10}F_3}$	1·000	1·084	1·100	1·112	273·1
		1·076	1·090	1·101	298·1
		1·053	1·062	1·076	400
		1·039	1·044	1·050	500
		1·030	1·033	1·038	600
			∞	∞	0
$\frac{B^{11}Cl_3\ (l.)}{B^{10}Cl_3\ (l.)}$		1·000	1·015	1·026	273·1
			1·013	1·023	298·1
			1·008	1·016	400
			1·005	1·011	500
			1·004	1·008	600
				0	0
$\frac{B^{11}Cl_3\ (g.)}{B^{10}Cl_3\ (g.)}$			1·000	1·011	273·1
				1·010	298·1
				1·008	400
				1·006	500
				1·004	600

TABLE VIII.

Carbon Exchange.

	$C^{13}O_3^{=}$ / $C^{12}O_3^{=}$	$C^{13}O_3^{-}$ / $C^{12}O_3^{-}$	C^{13} * / C^{12} *	$HC^{13}N$ / $HC^{12}N$	$C^{13}O$ / $C^{12}O$	$C^{13}N^{-}$ / $C^{12}N^{-}$	T, ° K.
Q_2 / Q_1	1·2358	1·2169	1·2081	1·1358	1·1086	1·0980	273·1
	1·2057	1·1909	1·1786	1·1206	1·0970	1·0875	298·1
	1·1274	1·1233	1·1077	1·0802	1·0659	1·0589	400
	1·0870	1·0877	1·0722	1·0581	1·0479	1·0427	500
	1·0629	1·0656	1·0516	1·0441	1·0360	1·0323	600
		∞		∞	∞	∞	0
$C^{13}O_3^{=}$ / $C^{12}O_3^{=}$	1·000	1·016	1·023	1·088	1·115	1·126	273·1
		1·012	1·023	1·076	1·099	1·109	298·1
		1·004	1·018	1·045	1·058	1·066	400
		$0·999_4$	1·014	1·027	1·037	1·042	500
		$0·997_5$	1·011	1·018	1·026	1·030	600
			0	∞	∞	∞	0
$C^{13}O_2$ / $C^{12}O_2$		1·000	1·007	1·071	1·098	1·108	273·1
			1·010	1·063	1·086	1·095	298·1
			1·014	1·040	1·055	1·061	400
			1·014	1·028	1·038	1·043	500
			1·013	1·021	1·029	1·032	600
				∞	∞	∞	0
C^{13} / C^{12}			1·000	1·064	1·090	1·100	273·1
				1·052	1·074	1·084	298·1
				1·025	1·039	1·046	400
				1·013	1·023	1·028	500
				1·007	1·015	1·017	600
					∞	∞	0
$HC^{13}N$ / $HC^{12}N$				1·000	1·025	1·034	273·1
					1·022	1·030	298·1
					1·013	1·020	400
					1·010	1·015	500
					1·008	1·011	600
						∞	0
$C^{13}O$ / $C^{12}O$					1·000	1·010	273·1
						1·009	298·1
						1·007	400
						1·005	500
						1·004	600

* The partition function recorded here is for diamond. The Debye θ's have been taken as 1860 and 1787 for C^{12} and C^{13} respectively. The partition functions have been calculated using the equations given by Mayer and Mayer, "Statistical Mechanics," John Wiley and Sons, New York, 1940.

equilibrium constant at the temperature shown in the far right column between the molecules listed at the top of the column and at the left. If these constants are greater than unity the heavier isotope will concentrate preferentially in the compound listed at the left. The blank part of the table could be filled with the reciprocals of the numbers listed.

In the case of the hydrogen exchange reactions as listed in Table V, the constants recorded are only approximate when H_2, D_2, T_2, and H_2O, D_2O, and T_2O are involved, since the equilibrium constants involving the mixed molecules are not approximately equal to 4. It is necessary to calculate the partition functions for the mixed molecules. The ratios of these partition functions and equilibrium constants are listed in Tables III and IV. The symbol Q_{12} refers to the mixed molecules, and the values of Q_1 and Q_2 for the homogeneous molecules are the squares of those listed in the main tables.

The constants listed in Table IV in which either H_2, D_2 or H_2O, D_2O are involved will give the exact ratio of isotopes when the concentrations of H_2 and D_2 in the hydrogen gas are equal or when the concentrations of H_2O and D_2O are equal in the water vapour.

The equilibrium constants listed in Table VI for lithium are few in number and do not deviate from unity as much as one might expect for this light element. The maximum deviation from unity in the case of boron is 0·112 whereas for lithium this is 0·033. It seems probable that considerable fractionation would occur between the very stable compounds of lithium such as the oxide and fluoride and, say, the metal vapour, but these compounds do not lend themselves either to spectroscopic investigations or to experimental exchange reaction studies.

The boron exchanges are limited to the boron halides. Of particular interest is the predicted difference in vapour pressures of the isotopic boron chlorides. In other cases in which Raman

TABLE IX.

Nitrogen Exchange.

	$N^{15}H_4^+/N^{14}H_4^+$	$(N_2^{15}/N_2^{14})^{\frac{1}{2}}$	$N^{15}H_3/N^{14}H_3$	$N^{15}O/N^{14}O$	HCN^{15}/HCN^{14}	CN^{-15}/CN^{-14}	T, ° K.
Q_2/Q_1	1·1184	1·0908	1·0768	$1·073_8$	1·0736	1·0718	273·1
	1·1059	1·0814	1·0688	$1·065_9$	1·0655	1·0641	298·1
	1·0721	1·0558	1·0472	$1·044_0$	1·0439	1·0433	400
	1·0530	1·0410	1·0350	$1·031_6$	1·0316	1·0315	500
	1·0409	1·0311	1·0271	$1·023_8$	1·0238	1·0239	600
		∞	∞	∞	∞	∞	0
$N^{15}H_4^+/N^{14}H_4^+$	1·000	1·025	1·039	1·042	1·042	1·043	273·1
		1·023	1·035	1·038	1·038	1·039	298·1
		1·015	1·024	1·027	1·027	1·028	400
		1·012	1·017	1·021	1·021	1·021	500
		1·010	1·013	1·017	1·017	1·017	600
			∞	∞	∞	∞	0
$(N_2^{15}/N_2^{14})^{\frac{1}{2}}$		1·000	1·013	1·016	1·016	1·018	273·1
			1·012	1·015	1·015	1·016	298·1
			1·008	1·011	1·011	1·012	400
			1·006	1·009	1·009	1·009	500
			1·004	1·007	1·007	1·007	600
				∞	∞	∞	0
$N^{15}H_3/N^{14}H_3$			1·000	1·003	1·003	1·005	273·1
				1·003	1·003	1·004	298·1
				1·003	1·003	1·004	400
				1·003	1·003	1·003	500
				1·003	1·003	1·003	600
					∞	∞	0
$N^{15}O/N^{14}O$				1·000	$1·000_2$	1·002	273·1
					$1·000_4$	1·002	298·1
					$1·000_1$	1·001	400
					$1·000_0$	1·000	500
					$1·000_0$	1·000	600
						∞	0
HCN^{15}/HCN^{14}					1·000	1·002	273·1
						1·001	298·1
						1·001	400
						1·000	500
						1·000	600

frequencies for the liquid and gaseous states have been observed as well as in this, the frequencies are usually lower for the liquid state and this should result in a preferential concentration of the heavier isotope in the gas phase. This is not true in this case because of the larger observed isotopic shift of the ω_3 frequency in the liquid as compared with the gas. If this is in error for some reason not evident from the paper by Anderson, Lassettre, and Yost, the predicted difference in vapour pressures will be incorrect, and in fact may be so because of the application of gaseous partition functions to the liquid state.

The equilibrium constants for chlorine exchange reactions are surprisingly large. This is due to the increased number of vibrational degrees of freedom as the number of oxygen atoms combined with the chlorine atom increases, and the approximate constancy of the vibrational frequencies of all the oxygen compounds of chlorine. Similar effects should occur in the case of the sulphur isotopes, and in fact the experimental values for their fractionation between sulphur dioxide and bisulphite ion are close to the corresponding value for the chlorine isotopes.*

The tables for chlorine, bromine, and iodine show the trend of these equilibrium constants with atomic weight for constant difference of atomic weight. The exchange constants for ClO_3^-, BrO_3^-, and IO_3^- and their corresponding elements at 298·1° are 1·040, 1·007, and 1·003, respectively. It is evident that these chemical differences decrease rapidly with atomic weight though there is considerable irregularity in many cases, as for example in the calculated values for lithium and those for chlorine. The iodine example using I^{129} has been included for the purpose of comparison.

The values of the equilibrium constants at 0° K. are either 0 or ∞ and depend on the zero-point energies only. When the equilibrium constants are nearly unity at higher temperatures

* That such large fractionation factors should exist was first called to my attention by Dr. Duane Vier, who made the calculation for the chlorine dioxide–chlorine exchange.

TABLE X.

Oxygen Exchange.

	$\left(\frac{CO_2^{18}}{CO_2^{16}}\right)^{\frac{1}{2}}$ ·	$\frac{CO^{18}}{CO^{16}}$ ·	$\left(\frac{CO_3^{18=}}{CO_3^{16=}}\right)^{\frac{1}{2}}$ ·	$\left(\frac{SO_4^{18=}}{SO_4^{16=}}\right)^{\frac{1}{2}}$ ·	$\left(\frac{SO_2^{18}}{SO_2^{16}}\right)^{\frac{1}{2}}$ ·	$\frac{D_2O^{18}}{D_2O^{16}}$ ·	$\left(\frac{O_2^{18}}{O_2^{16}}\right)^{\frac{1}{2}}$ ·	$\frac{H_2O^{18}}{H_2O^{16}}$ ·	$\left(\frac{ClO_2^{18}}{ClO_2^{16}}\right)^{\frac{1}{2}}$ ·	T, ° K.
Q_2	1·1331	1·1181	1·1090	1·1073	1·1017	1·0974	1·0923	1·0741	1·0717	273·1
Q_1	1·1172	1·1053	1·0945	1·0924	1·0888	1·0872	1·0818	1·0667	1·0621	298·1
	1·0750	1·0714	1·0576	1·0557	1·0551	1·0594	1·0533	1·0465	1·0375	400
	1·0525	1·0518	1·0388	1·0370	1·0376	1·0437	1·0374	1·0350	1·0251	500
	1·0387	1·0390	1·0279	1·0261	1·0271	1·0336	1·0274	1·0275	1·0179	600
		∞	∞	0	∞	∞	∞	∞	∞	0
$\left(\frac{CO_2^{18}}{CO_2^{16}}\right)^{\frac{1}{2}}$	1·000	1·013	1·022	1·023	1·029	1·033	1·037	1·055	1·057	273·1
		1·011	1·021	1·023	1·026	1·028	1·033	1·047	1·052	298·1
		1·003	1·016	1·018	1·020	1·015	1·021	1·027	1·036	400
		1·000$_7$	1·013	1·015	1·014	1·008	1·016	1·017	1·027	500
		0·999$_7$	1·011	1·012	1·011	1·005	1·011	1·011	1·020	600
			0	0	0	∞	∞	∞	∞	0
$\frac{CO^{18}}{CO^{16}}$		1·000	1·008	1·010	1·015	1·019	1·024	1·041	1·043	273·1
			1·010	1·012	1·015	1·017	1·022	1·036	1·041	298·1
			1·013	1·015	1·015	1·011	1·017	1·024	1·033	400
			1·014	1·014	1·014	1·008	1·014	1·016	1·026	500
			1·011	1·013	1·012	1·005	1·011	1·011	1·021	600
				0	∞	∞	∞	∞	∞	0
$\left(\frac{CO_3^{18=}}{CO_3^{16=}}\right)^{\frac{1}{2}}$			1·000	1·002	1·007	1·011	1·015	1·033	1·035	273·1
				1·002	1·005	1·007	1·012	1·026	1·031	298·1
				1·002	1·002	0·998	1·004	1·011	1·019	400
				1·002	1·001	0·995	1·001	1·004	1·013	500
				1·002	1·001	0·994	1·000	1·000$_4$	1·010	600
					∞	∞	∞	∞	∞	0
$\left(\frac{SO_4^{18=}}{SO_4^{16=}}\right)^{\frac{1}{2}}$				1·000	1·005	1·009	1·014	1·031	1·033	273·1
					1·003	1·005	1·010	1·024	1·029	298·1
					1·001	0·997	1·002	1·009	1·018	400
					0·999	0·994	0·999$_6$	1·003	1·012	500
					0·999	0·993	0·999	0·999	1·008	600
						∞	∞	∞	∞	0
$\left(\frac{SO_2^{18}}{SO_2^{16}}\right)^{\frac{1}{2}}$					1·000	1·004	1·007	1·026	1·028	273·1
						1·001	1·006	1·021	1·025	298·1
						0·996	1·003	1·008	1·017	400
						0·994	1·000	1·003	1·012	500
						0·994	0·999$_7$	0·999$_8$	1·009	600
							0	∞	∞	0
$\frac{D_2O^{18}}{D_2O^{16}}$						1·000	1·005	1·022	1·024	273·1
							1·005	1·019	1·024	298·1
							1·006	1·013	1·021	400
							1·006	1·008	1·018	500
							1·006	1·006	1·015	600
								∞	∞	0
$\left(\frac{O_2^{18}}{O_2^{16}}\right)^{\frac{1}{2}}$							1·000	1·017	1·019	273·1
								1·014	1·019	298·1
								1·006	1·015	400
								1·002	1·012	500
								0·999$_9$	1·009	600
									0	0
$\frac{H_2O^{18}}{H_2O^{16}}$								1·000	1·002	273·1
									1·004	298·1
									1·009	400
									1·010	500
									1·009	600

these values for 0° K. may easily be in error since a small error in estimating the zero point energy could change these from 0 to ∞ or the reverse.

Experimental Confirmation of the Calculations.

Of the many equilibrium constants calculated, only a few have been checked by experiment. Most of these cannot be confirmed because no method of establishing equilibrium is possible owing to the slowness with which equilibrium is established or because chemical reactions occur between the chemical compounds involved. The equilibrium between H_2, I_2, and HI was compared by Urey and Rittenberg [24] with that between D_2, I_2, and DI and the ratio of

TABLE XI.

Chlorine Exchange.

	$\frac{Cl^{37}O_4^-}{Cl^{35}O_4^-}$.	$\frac{Cl^{37}O_3^-}{Cl^{35}O_3^-}$.	$\frac{Cl^{37}O_2}{Cl^{35}O_2}$.	$\left(\frac{Cl_2^{37}}{Cl_2^{35}}\right)^{\frac{1}{2}}$.	$\frac{HCl^{37}}{HCl^{35}}$.	T, ° K.
$\frac{Q_2}{Q_1}$	1·0972	1·0551	1·0360	1·0086	1·0050	273·1
	1·0847	1·0478	1·0313	1·0074	1·0046	298·1
	1·0521	1·0291	1·0185	1·0043	1·0032	400
	1·0353	1·0196	1·0130	1·0028	1·0024	500
	1·0253	1·0140	1·0094	1·0019	1·0019	600
		∞	∞	∞	∞	0
$\frac{Cl^{37}O_4^-}{Cl^{35}O_4^-}$	1·000	1·040	1·059	1·088	1·092	273·1
		1·035	1·052	1·077	1·080	298·1
		1·022	1·033	1·048	1·049	400
		1·015	1·022	1·032	1·033	500
		1·011	1·016	1·023	1·023	600
			∞	∞	∞	0
$\frac{Cl^{37}O_3^-}{Cl^{35}O_3^-}$		1·000	1·018	1·046	1·050	273·1
			1·016	1·040	1·043	298·1
			1·010	1·025	1·026	400
			1·007	1·017	1·017	500
			1·005	1·012	1·012	600
				∞	∞	0
$\frac{Cl^{37}O_2}{Cl^{35}O_2}$			1·000	1·027	1·031	273·1
				1·024	1·027	298·1
				1·014	1·015	400
				1·010	1·010	500
				1·007	1·007	600
					∞	0
$\left(\frac{Cl_2^{37}}{Cl_2^{35}}\right)^{\frac{1}{2}}$				1·000	1·004	273·1
					1·003	298·1
					1·001	400
					$1·000_4$	500
					$1·000_0$	600

TABLE XII.

Bromine Exchange.

	$\frac{Br^{81}O_3^-}{Br^{79}O_3^-}$.	$\left(\frac{Br_2^{81}}{Br_2^{79}}\right)^{\frac{1}{2}}$.	$\frac{HBr^{81}}{HBr^{79}}$.	T, ° K.
$\frac{Q_2}{Q_1}$	1·0093	1·0014	1·0009	273·1
	1·0080	1·0012	1·0008	298·1
	1·0048	1·0007	1·0006	400
	1·0032	1·0004	1·0004	500
	1·0022	1·0003	1·0003	600
		∞	∞	0
$\frac{Br^{81}O_3^-}{Br^{79}O_3^-}$	1·000	1·008	1·008	273·1
		1·007	1·007	298·1
		1·004	1·003	400
		1·003	1·003	500
		1·002	1·002	600
			∞	0
$\left(\frac{Br_2^{81}}{Br_2^{79}}\right)^{\frac{1}{2}}$		1·000	$1·000_5$	273·1
			$1·000_4$	298·1
			$1·000_1$	400
			$1·000_0$	500
			$1·000_0$	600

TABLE XIII.

Iodine Exchange.

	$\frac{I^{129}O_3^-}{I^{127}O_3^-}$.	$\left(\frac{I_2^{129}}{I_2^{127}}\right)^{\frac{1}{2}}$.	T, ° K.
$\frac{Q_2}{Q_1}$	1·0031	1·0003	298·1
		∞	0
$\frac{I^{129}O_3^-}{I^{127}O_3^-}$	1·0000	$1·002_5$	298·1

equilibrium constants agreed with those calculated for the exchange reaction. Several authors [25] have investigated the equilibrium between H_2, HD, H_2O, and HDO and given several values which are in rough agreement with the calculated results. Libby [26] has calculated the equilibrium constants for the hydrogen–water exchanges with respect to protium, deuterium, and tritium, and he and Taylor and Black have checked these calculations for the protium–tritium exchange with excellent agreement. The equilibrium constants given here differ slightly from Libby's owing to the inclusion of rotational corrections in some cases and to small errors made by Libby (see corrections in forthcoming issue of the *J. Chem. Physics*). The present calculations still do not include the rotational corrections for the water molecules and they also neglect small corrections for the anharmonicities. They agree better with experiment than do Libby's. Calculations were made by using anharmonic terms calculated by the Dennison and Darling rule and slightly better agreement with experiment was secured. Since there is a consistent difference between calculated and the experimental values, there is probably a systematic error present. On the theoretical side, this may be due to errors in the anharmonic terms or to electronic isotope effects, though both of these should lead to a constant percentage error with temperature and not a constant difference which appears to be the case. Since the equilibrium constants for the hydrogen exchange reactions must include all corrections discussed in this paper, exact calculations cannot be made without a full knowledge of the structure of the molecules, and for this reason exact agreement between calculated and observed values cannot be expected for many feasible reactions.

These reactions, as well as others that have been studied, are listed in Table XIV. All the reactions involving other isotopes than those of hydrogen are two-phase reactions and, except for the first for which the relative vapour pressures are known, exact agreement cannot be expected. Reasonably satisfactory agreement is secured, and in the case of those reactions for which spectroscopic data are lacking, fractionation of the isotopes of the correct order of magnitude is observed. Some of the observed values are derived from isotope separation

TABLE XIV.

Reaction.	T, ° K.	α (exp.).	α (calc.).	Ref.
$\frac{1}{3}CO_3^{16} + H_2O^{18}$ (liq.) $= \frac{1}{3}CO_3^{18} + H_2O^{16}$ (liq.)	273·1	1·046	1·044	(1)
$N^{15}H_3 + N^{14}H_4^+ = N^{14}H_3 + N^{15}H_4^+$	298·1	1·034±0·002	1·035	(2)
$N^{15}H_3 + N^{14}H_3$ (aq.) $= N^{14}H_3 + N^{15}H_3$ (aq.)	298·1	1·006±0·002	—	(2)
$HC^{13}N + C^{13}N^- = HC^{13}N + C^{12}N^-$	295*	Near 1·026	1·030	(3)
$HCN^{14} + CN^{15-} = HCN^{15} + CN^{14-}$	295 *	Slightly <1	1·002	(4)
$C^{12}O_3^{=} + C^{12}O_2 = C^{13}O_3^{=} + C^{12}O_2$.....	273·1?	1·017	1·016	(5)
$\frac{1}{3}CO_3^{16=} + H_2O^{18} = \frac{1}{3}CO_3^{18=} + H_2O^{16}$	273·1?	1·036	1·033	(6)
$HC^{12}O_3^- + C^{13}O_2 = HC^{13}O_3^- + C^{12}O_2$	298 *	>1·014	—	(7)
$S^{34}O_2 + HS^{32}O_3^- = S^{32}O_2 + HS^{34}O_3^-$	298·1	1·019±0·002	—	(2)
$S^{34}O_2 + HS^{32}O_3^- = S^{32}O_2 + HS^{34}O_3^-$	298·1	1·043±0·004	—	(2)
$Li^7Z + Li^{6+} = Li^6Z + Li^{7+}$	295 *	1·022	—	(8)
Li^7 (amal.) + $Li^6Cl = Li^6$ (amal.) + Li^7Cl	295 *	1·025	—	(9)
$HD + H_2O = HDO + H_2$	293	3·2	3·81	(10)
$HD + H_2O = HDO + H_2$	800	1·28	1·36	(11)
$HT + H_2O = HTO + H_2$	273·1	7·74	7·64	(12)
,, ,, ...	298·1	6·26	6·19	(12)
,, ,, ...	400	3·52	3·46	(12)
,, ,, ...	500	2·55	2·47	(12)
,, ,, ...	600	2·08	1·99	(12)

* These temperatures are assumed to be 72° F., *i.e.*, the usual room temperature in the U.S.

(1) Weber, Wahl, and Urey, *J. Chem. Physics*, 1935, **3**, 129.
(2) Thode, Graham, and Ziegler, *Canadian J. Res.*, 1945, **23***B*, 40; Kirschenbaum and others, in the press. The latter authors have extrapolated the values of Thode *et al.* to zero concentration of NH_3 in the solution. The constant 1·006 is the average of those reported by these authors.
(3) Cohen, *J. Chem. Physics*, 1940, **8**, 588.
(4) Hutchison, Stewart, and Urey, *ibid.*, p. 532.
(5) Nier and Gulbransen, *J. Amer. Chem. Soc.*, 1939, **61**, 697; Murphey and Nier, *Physical Rev.*, 1941, **59**, 771.
(6) Dole and Slobod, *J. Amer. Chem. Soc.*, 1940, **62**, 471.
(7) Urey, Aten, junr., and Keston, *J. Chem. Physics*, 1936, **4**, 622.
(8) Taylor and Urey, *ibid.*, 1938, **6**, 429.
(9) Lewis and MacDonald, *J. Amer. Chem. Soc.*, 1936, **58**, 2519.
(10) Bonhoeffer, *Z. Elektrochem.*, 1934, **40**, 469.
(11) Crist and Dalin, *J. Chem. Physics*, 1934, **3**, 735.
(12) Black and Taylor (*loc. cit.*) give a formula covering data between 16° C. and 302·9° C. from which the "experimental" data of the table have been calculated. They estimate their probable errors as ±0·02 to ±0·12 and thus theory and experiment are in agreement within these limits.

experiments under conditions which must give results lower than the true values. It is seen that good agreement is secured. The results of Thode and his co-workers are based on very careful work.

Vapour Pressures of Isotopic Compounds.

The ratios of vapour pressures of hydrogen and deuterium and their compounds have been extensively studied.[27] Similar differences in vapour pressures in the case of isotopic molecules of other elements exist, though the differences are much smaller than in the case of protium and deuterium compounds. Such differences have been determined in only a few cases and are recorded in Table XV together with those for protium and deuterium oxide and the protium and deuterium ammonias for comparison. In the last column are given the temperatures at which the vapour pressures are equal. These are calculated from the formulæ in all cases except for H_2O and D_2O. This " crossing-over phenomenon " seems to be a regular feature of all such ratios of vapour pressures. Bernal and Tamm [28] have assumed that a frequency of libration of the water molecule in ice of 477 cm.$^{-1}$ exists and that this accounts for the differences in vapour pressures of H_2O and D_2O. However, it does not account for the " crossing-over phenomenon " and it seems clear that much more extensive theories to account for the ratio of vapour-pressure curve are required. It is interesting to note that this same " crossing-over phenomenon " exists for some exchange reactions as mentioned before, and that it can be calculated in these cases though no obvious similar method can be applied to the vapour pressures.

The vapour pressures of N_2^{14} and N_2^{15} suggest the possibility of an excellent separation method for the oxygen isotopes. Since carbon monoxide and nitrogen have such similar physical properties, similar differences in vapour pressure might be expected between $C^{12}O^{16}$ and $C^{13}O^{18}$ for which a difference of two atomic weight units exists as in the case of the nitrogens. If a difference of 1% in vapour pressures exists, distillation of carbon monoxide should furnish the most effective method for the separation of these isotopes and at the same time increase the concentration of the carbon isotope to some extent.

Also, if the predicted difference in vapour pressures of $B^{10}Cl_3$ and $B^{11}Cl_3$ can be confirmed, the distillation of boron chloride should be a most effective method for separating the isotopes of boron.

TABLE XV.

$$\log_{10}\frac{p_1}{p_2} = \frac{a}{T} + b.$$

Compounds.	*a*.	*b*.	Δ^2H.	$\Delta T.P.$	$\frac{p_1}{p_2}$ (b.p.).	$T(p_1 = p_2)$.	Ref.
N_2^{14},N_2^{15} (liq.)	0·7230	−0·005822	3·33	0·058	1·0081	124°	(1)
$N^{14}H_3$,$N^{15}H_3$ (liq.) ...	1·3665	−0·004622	6·25	0·188	1·00246	298	(2)
NH_3,ND_3 (liq.)	46·25	−0·14003	216	3·11	1·110	330·3	(1)
NH_3,ND_3 (sol.)	49·69	−0·1305	227·5	3·11	—	—	(1)
H_2O^{16},H_2O^{18} (liq.) ...	2·74	−0·0056	13	—	1·0046	490	(3)
H_2O,D_2O (liq.)	†	†	406 *	3·8	1·051	497 (obs.)	(4)

* Value at the triple point according to Riesenfeld and Chang.

† Miles and Menzies give the following equation for the ratio of vapour pressures:

$$\log\frac{p_1}{p_2} = \frac{268{\cdot}8426}{T} - 16{\cdot}998671 + 7{\cdot}49716\log T - 9{\cdot}7611\times10^{-3}T + 4{\cdot}4288\times10^{-6}T^2.$$

(1) Kirschenbaum and Urey, *J. Chem. Physics*, 1942, **10**, 706.
(2) Thode, *J. Amer. Chem. Soc.*, 1940, **62**, 1581.
(3) Riesenfeld and Chang, *Z. physikal Chem.*, 1936, *B*, **33**, 127.
(4) *Idem, ibid.*, p. 120; Miles and Menzies, *J. Amer. Chem. Soc.*, 1936, **58**, 1068.

In many cases the equilibrium constants of exchange reactions involving liquid water rather than gaseous water are desired. The equilibrium constants of Table V and Table X involving water must be increased in the horizonal rows and decreased in the vertical columns in the ratio of the vapour pressures of H_2O^{16} and H_2O^{18} or the square root of the ratio of H_2O and D_2O in order to secure the constants for liquid water. These ratios at temperatures (K.) 273·1°, 298·1°, and 400° are for H_2O^{16} and H_2O^{18}, 1·011, 1·008 and 1·003, and for H_2O and D_2O, 1·102, 1·074, and 1·017, respectively.

The Geological Abundances of the Carbon and Oxygen Isotopes.

Dole and Nier and their co-workers have determined the ratio of the oxygen and carbon isotopes in various geological deposits. The carbonates are of particular interest in connection with the calculations presented here. It is not possible to calculate the Q_2/Q_1 values for the carbon and oxygen isotopes in the carbonates with certainty, for the formulæ for the vibration

frequencies using a quadratic formula for the potential energy [29] require five constants for the determination of four frequencies and none of the central force or valence force formulæ gives satisfactory results since the force constants calculated from the observed frequencies are complex. Even if satisfactory agreement were secured, there would be no certainty that the isotopic shifts in frequencies calculated would be correct, as is also true in other cases. In view of this difficulty, another approach to the problem has been used.[30]

The experimental facts are briefly that O^{18} is more abundant in limestones than in water by a factor of 1·035, and C^{13} is also more abundant in carbonates of all geological ages including the present than in atmospheric carbon dioxide, by a factor of 1·013 to 1·022, as shown by Nier. There is a slight disagreement between the results of Nier and Gulbransen and of Murphy and Nier.[31]

No satisfactory calculation of the constants for the exchange constants for the reactions

$$\tfrac{1}{2}C^{13}O_2 + \tfrac{1}{3}C^{12}O_3^{=} = \tfrac{1}{2}C^{12}O_2 + \tfrac{1}{3}C^{13}O_3^{=} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

and

$$H_2O^{18} + \tfrac{1}{3}CO_3^{16=} = H_2O^{16} + \tfrac{1}{3}CO_3^{18=} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

can be made, but it is possible to ask whether the two observed values are consistent with each other. There is no difficulty in calculating the isotopic shifts for frequencies ν_1 (symmetrical vibrations of the oxygen atoms in the plane of the molecule) and ν_2 (vibration perpendicular to the plane of the molecule), but the doubly degenerate frequencies ν_3 and ν_4 cannot be calculated since three constants are required in the potential-energy functions.

Rosenthal shows that the formula for the frequencies ν_3 and ν_4 is

$$m^2\lambda^2 - m\lambda\,(\tfrac{1}{3}\,A/\mu + D) + (1/\mu)\,(AD - E^2) = 0 \quad . \quad . \quad . \quad . \quad . \quad (16)$$

where the roots of this equation, λ_3 and λ_4, are $4\pi^2\nu_3^2$ and $4\pi^2\nu_4^2$; m is the mass of the oxygen atom and $\mu = M/(M + 3m)$, M being the mass of the carbon atom. Solving for λ_3 and λ_4 and forming

$$\frac{\partial \ln \lambda_3}{\partial M}, \quad \frac{\partial \ln \lambda_4}{\partial M}, \quad \frac{\partial \ln \lambda_3}{\partial m} \quad \text{and} \quad \frac{\partial \ln \lambda_4}{\partial m},$$

it is easily possible to eliminate all force constants between the expressions

$$\frac{\partial \ln \lambda_3}{\partial M} \quad \text{and} \quad \frac{\partial \ln \lambda_4}{\partial m} \quad \text{and between} \quad \frac{\partial \ln \lambda_4}{\partial M} \quad \text{and} \quad \frac{\partial \ln \lambda_4}{\partial m}.$$

Then, replacing $\dfrac{\partial \ln \lambda_3}{\partial M}$, etc., by the approximate values $\dfrac{\Delta\lambda_3}{\Delta M \lambda_3}$, etc., the following relations are secured:

$$-\left(\frac{\Delta\nu_3}{\nu_3}\right)_0 = \frac{\Delta m}{2m} + \frac{M\Delta m}{m\Delta M}\left(\frac{\Delta\nu_3}{\nu_3}\right)_C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

and

$$-\left(\frac{\Delta\nu_4}{\nu_4}\right)_0 = \frac{\Delta m}{2m} + \frac{M\Delta m}{m\Delta M}\left(\frac{\Delta\nu_4}{\nu_4}\right)_C \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

where the $\Delta\nu$'s are negative quantities when the Δm and ΔM are positive.[31a] By using the last term of equation (16) and noting that it is $m^2\lambda_3\lambda_4$, we get,

$$\ln \lambda_3\lambda_4 = -2 \ln m + \ln (M + 3m) - \ln M + \ln (AD - E^2)$$

By expanding the right-hand side of this equation in terms of Δm or ΔM and substituting numerical values for m and M, we secure

$$\left(\frac{\Delta\nu_3}{\nu_3}\right)_0 + \left(\frac{\Delta\nu_4}{\nu_4}\right)_0 = -0{\cdot}0703 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

and

$$\left(\frac{\Delta\nu_3}{\nu_3}\right)_C + \left(\frac{\Delta\nu_4}{\nu_4}\right)_C = -0{\cdot}031667 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

Urey and Greiff used frequencies calculated by Dr. Rosenthal for $C^{13}O_3^{=}$ and these frequencies agree with the requirement of equation (20). It is possible to choose values for $\left(\dfrac{\Delta\nu_3}{\nu_3}\right)_C$ and $\left(\dfrac{\Delta\nu_4}{\nu_4}\right)_C$ consistent with equation (20) and then calculate values for $\left(\dfrac{\Delta\nu_3}{\nu_3}\right)_0$ and $\left(\dfrac{\Delta\nu_4}{\nu_4}\right)_0$. From these quantities we can now calculate the Q_2/Q_1 values and from them and the values of Q_2/Q_1

for H_2O^{18}–H_2O^{16}, and CO_2^{18}–CO_2^{16} the equilibrium constants for the reactions (14) and (15). Table XVI gives the results of such a calculation for three arbitrary choices of $\left(\frac{\Delta\nu_3}{\nu_3}\right)_C$, the one choice 0·03109 being that secured by Rosenthal, and for two temperatures 273·1° K. and 298·1° K.

TABLE XVI.

$\left(\frac{\Delta\nu_2}{\nu_2}\right)_C$	0·03107	0·030	0·0285	$\left(\frac{Q_2}{Q_1}\right)_C$ (273·1)	1·2406	1·2358	1·2291
$\left(\frac{\Delta\nu_4}{\nu_4}\right)_C$	0·000576	0·001667	0·003167	$\left(\frac{Q_2}{Q_1}\right)_0$ (273·1)	1·1068	1·1090	1·1120
$\left(\frac{\Delta\nu_2}{\nu_2}\right)_0$	0·013103	0·014707	0·016912	$\left(\frac{Q_2}{Q_1}\right)_0$ (298·1)	1·2097	1·2057	1·1997
$\left(\frac{\Delta\nu_4}{\nu_4}\right)_C$	0·057976	0·056374	0·054168	$\left(\frac{Q_2}{Q_1}\right)_0$ (298·1)	1·0928	1·0947	1·0979
$(\Delta\nu_3)_C$	44·68	43·11	40·95	K_C (273·1) ...	1·0195	1·0156	1·0101
$(\Delta\nu_4)_C$	0·41	1·19	2·26	K_C (298·1) ...	1·0158	1·0123	1·0073
$(\Delta\nu_3)_0$	18·83	21·13	24·30	K_0 (273·1) ...	1·0304	1·0325	1·0353
$(\Delta\nu_4)_0$	41·40	40·25	38·68	K_0 (298·1) ...	1·0245	1·0261	1·0288

Dole's value for the difference in density of water from the tap at Northwestern University and water prepared from carbon dioxide from Grenville limestone is 7·9 p.p.m. or a ratio of isotopes of 1·0356 greater than his standard water. If we assume that fresh water has the same composition as water vapour from the oceans, then this is directly the ratio which we have calculated. This assumption seems to be in as close accord with experimental determination of the differences in density between ocean water and fresh water as any other. Nier's values for the enrichment of C^{13} in carbonates range from 1·013 to 1·021. We will take 1·0175 as a reasonable value. Then the calculations of Table XVI for 0° c. indicate that the values for $(\Delta\nu_3/\nu_3)_C = 0{\cdot}030$ are best, but both are lower than the experimental values. Also, the values calculated at 25° c. are lower, but also $(\Delta\nu_3/\nu_3)_C = 0{\cdot}030$ gives the best fit to the data. Hence this value is chosen as the best fit with experiment and all Q_2/Q_1 ratios of Tables VIII and X are made on this basis.

The discrepancy between the calculated and the observed values is not surprising in view of the neglect of anharmonic terms, and the application of partition functions for gaseous substances to the solid state. It seems unnecessary at present to suggest other explanations for the disagreement. It may be noted that the organisms which lay down carbonate use oxygen for their metabolic processes which contains more O^{18} than would be in equilibrium with water, but according to present beliefs in regard to biological oxidation the oxygen of the carbon dioxide produced comes from the water and, hence, no increase in O^{18} content should come from this source.

These calculations suggest investigations of particular interest to geology. A change from 0° c. to 25° c. should change the O^{18} content of carbonate by 1·004 relative to liquid water and the C^{13} content by 1·003. Accurate determinations of the O^{18} content of carbonate rocks could be used to determine the temperature at which they were formed. Since the relative abundances of isotopes have been determined by Dole with a probable error of less than 0·002 and Thode has made mass-spectrometric measurements with the same probable error, it is possible to determine such a temperature within 12° c. Nier has developed a mass spectrometer which will determine these ratios with an error of $\pm$ 0·001 and very probably less, and thus an error in temperature of only 6° C. or less is possible. This would be a very satisfactory error in temperature considering the times to which they may refer. At higher temperatures the coefficient becomes smaller, but still it may be possible to determine temperatures with sufficient precision to supply valuable data on a very difficult problem.

There are many questions which arise in regard to this suggestion in addition to whether animals lay down carbonates in equilibrium with water. It is not certain that the carbonates once deposited do not exchange their oxygen with ground water at a temperature different from the original or of isotopic composition different from that of sea water. Diffusion processes in carbonate rocks must be slow but the carbonates may be porous and finely divided. Such questions are all subject to experimental investigation, as is also the experimental determination of the true temperature coefficient. Even the present calculation and experimental observations indicate that the earth's temperature has not changed greatly in the last odd billion years. Also, the O^{18} content of carbonates deposited in fresh water should be less than that deposited in sea water and might be used to distinguish fresh and salt-water deposits.[32] The use of

the C^{13} content of rocks would be more difficult because of the smaller enrichment and also because the geological history of carbon must be far more complex than that of oxygen. While the oxygen of the oceans constitutes a very large reservoir for the deposition of carbonate and hence has not changed its isotopic composition with time, carbon is a much rarer element and the carbon dioxide of the air and the ocean is part of the complex biochemical carbon cycle of Nature. However, the abundance of C^{13} in the rocks, if sufficiently accurately determined, might give additional data on the amount of carbon dioxide in the air during past epochs, particularly if combined with accurate temperature determinations by the use of the O^{18} content of the carbonates.

The oxygen isotopic abundances seem to be best suited for the determination of temperatures. First, there is the large reservoir of oxygen in the oceans which cannot have changed in isotopic concentrations during geological times. Secondly, the ideal isotopic solutions both solid and liquid make possible continuous variations of composition with temperatures. Thirdly, it is possible to determine deviations in isotopic abundances with considerable precision. Fourthly, oxygen forms relatively stable compounds which might be expected to remain unchanged for long periods of time. Ordinary chemical equilibria do not meet these conditions. The hydrogen compounds fail with respect to the third and the fourth point. Other elements fail with respect to the first and, hence, are not suitable. Calcium is widely distributed in Nature but fails with respect to the first point.

Dole has studied the relative abundances of the oxygen isotopes in iron ores and finds but a slight difference between them and the abundances in fresh water. A determination of the relative abundances in freshly deposited iron oxide and a comparison of these with geological deposits might give information in regard to the conditions under which such deposits were laid down.

Other oxygen compounds besides carbonates and iron oxides are available for similar studies. The exchange between sulphate and water shows a similar temperature coefficient to that between carbonate and water, and similar coefficients for the phosphate and water and the silica and water exchanges are to be expected. These last two are particularly interesting because animals and plants deposit both of these substances and also since silica has been deposited inorganically from solutions. In some cases connate water has been preserved, thus supplying both phases for investigation.

Nier and his co-workers have found that C^{13} is rarer in carbon derived from plants than it is in carbon dioxide of the air or carbon from the carbonate rocks. Such variations must result from biochemical processes which are far more complex than those considered here, and it seems that they are probably not due to thermodynamic equilibria alone but rather to differences in the kinetics of such processes. Nevertheless, the variation of kinetic processes with temperature may also result in different abundances of the isotopes. It seems probable that plant carbon compounds synthesised at different temperatures may contain varying amounts of C^{13}. Again, this possibility is subject to experimental investigation. It would be interesting indeed to know not only the mean temperature but also the variations of temperature on an ancient beach or in the forests where coal was deposited and whether a prehistoric animal had warm blood or not. However, too much optimism is not justified, for all the thermometers may be destroyed.

The values of $(\Delta\nu_3 + \Delta\nu_4)$ for the carbon isotopes can vary from 45·5 to 22·6, and for the oxygen isotopes from 59·6 to 93·3, and hence wide variations of equilibrium constants may be secured all consistent with the general equation, and since our choice of $(\Delta\nu_3/\nu_3)_C$ is near the maximum and $(\Delta\nu_4/\nu_4)_C$ is near the minimum value, it may be that similar extreme cases may occur in the case of other molecules. Hence, all calculations of this kind in which less independent force constants are used to calculate the frequencies than the number required for the potential-energy function using all quadratic terms may be in error by substantial amounts. This statement applies to all polyatomic molecules considered except CO_2, HCN, NH_4^+, and H_2O, for which all constants are known.

The Relative Abundances of the Oxygen Isotopes in Air and Water.

Extensive studies in regard to the relative abundances of the oxygen isotopes in the oxygen of the air and natural waters of the earth have been reported. Dole [33] first reported that water made from oxygen of the air was more dense than fresh water by 6·6 parts per million. This difference has been confirmed by other workers.[34] There is some disagreement in regard to the difference in density of fresh water and sea water due to the O^{18} content, but the values reported indicate about 2 parts per million, which is in reasonable agreement with the relative vapour pressures of H_2O^{16} and H_2O^{18}, assuming that fresh water is less dense because it results from

evaporation of sea water. Again, assuming that fresh water has the composition of water vapour in equilibrium with ocean water, Dole's observed difference should agree with that calculated here. The equilibrium constants for exchange between oxygen and gaseous water from Table X at 273·1° K. and 298·1° K. are 1·017 and 1·014 respectively, while Dole's observed value corresponds to 1·030, and hence agreement with the assumption of equilibrium between air oxygen and ocean water is not secured. If equilibrium with fresh water is assumed, the disagreement is even greater. These calculated values are considerably less than those calculated by Urey and Greiff, the change being due to new values for the frequencies of the water molecule. Since the constants for H_2O and O_2 are known in complete detail, it does not seem probable that the calculated values will be altered much by future changes in these constants. Other explanations for this effect have been proposed and are reviewed by Kamen [35] and since the calculations here contribute nothing new to the previous discussion, no review of the problem will be made here.

The Atomic Weights of the Elements.

The variations in relative abundances of the isotopes of the elements cause corresponding variations in the chemical atomic weights. These are small in all cases but have been observed in the case of hydrogen and oxygen and should be observable in the case of chlorine. The observed constancy of the atomic weights in the case of these elements must be due to the selection of the same source for the element and the careful duplication of purification procedures. The largest changes in atomic weights to be expected from the equilibrium constants given in the tables for the various elements are given in Table XVII. Since the standard of chemical atomic weights varies, the same uncertainty enters into all the atomic weights. Fortunately the variability is low and in fact so low that no important error in chemical work will occur. The calculated change in the atomic weight of chlorine is surprisingly large.

TABLE XVII.

Calculated Maximum Variations in Atomic Weights.

Hydrogen *	0·00047	Nitrogen	0·00016
Lithium	0·0022	Oxygen	0·0023
Boron	0·016	Chlorine	0·031
Carbon	0·0014	Bromine	0·004

* In this case the water–hydrogen equilibrium at 0° C. is used rather than the water–potassium hydride equilibrium.

Application to the Separation of Isotopes.

During the past twenty-five years several interesting methods for the separation of isotopes have been devised, including the centrifugal, electromagnetic, and thermal and pressure diffusion of gases, and the electrolytic mobility method. These differences in chemical properties furnish another method for effecting such separations. Like all chemical methods, they are very specific, so that each element presents a separate and distinct research problem. Counter-current methods are necessary in order to secure large changes in concentration. These require two-phase systems and necessitate some convenient reflux reaction at the end of the apparatus where the desired isotope concentrates. When these conditions can be met, these chemical methods constitute very effective means for separating isotopes in quantity. Exchange reactions have been used for the concentration of D, Li, C^{13}, N^{15}, and S^{34} by reactions listed in Table XIV.[36] Also the differences in vapour pressures of isotopic compounds have been utilised for the concentration of D and O^{18}.[37] Unless the fractionation factors are about 1·01 or greater, these methods are difficult to use both because of the large size of the apparatus required and the expense of operation and because the times required for the apparatus to reach the steady state appropriate for continuous production become very large.

Conclusion.

Before the discovery of isotopes, it was generally assumed that all atoms of an element were identical in all respects. With their discovery it was evident that such atoms may differ in atomic weights, but it was believed that their chemical and physical properties were identical except for those properties directly related to mass such as densities of gases and condensed phases, rates of diffusion and evaporation, and others of this kind. As a result of the theoretical and experimental studies reviewed in this paper, we now know that isotopes and isotopic compounds differ in their thermodynamic properties. These differences are small except in the case of the hydrogens and they generally decrease with increasing atomic weight. These

small differences make possible the concentration and separation of the isotopes of some of the elements and may have important applications as a means of determining the temperatures at which geological formations were laid down.

My best thanks are due to Mr. L. S. Myers for his help in making the many calculations recorded in the tables of this paper.

[1] *Amer. J. Sci.*, 1906, **22**, 537; 1907, **24**, 370.
[2] Keetman, *Jahrb. Radioaktivität*, 1909, **6**, 265; Marckwald and Keetman, *Ber.*, 1908, **41**, 49; see also Hahn, *Ber.*, 1907, **40**, 4415.
[3] *Wien. Ber.*, 1910, iia, **119**, 1011.
[4] *Ber.*, 1910, **43**, 3420.
[5] *J.*, 1911, **99**, 72.
[6] *Phil. Mag.*, 1919, **37**, 523; **38**, 173.
[7] *Proc. Roy. Acad. Amsterdam*, 1931, **34**, 42; 1934, **37**, 615; 1935, **38**, 809.
[8] *Physical Rev.*, 1931, **39**, 164; 1932, **40**, 1.
[9] *J. Amer. Chem. Soc.*, 1933, **55**, 2616.
[10] *J. Chem. Physics*, 1933, **1**, 137.
[11] *Proc. Roy. Soc.*, 1934, *A*, **144**, 467.
[12] *J. Amer. Chem. Soc.*, 1935, **57**, 321.
[13] Scott, Brickwedde, Urey, and Wahl, *J. Chem. Physics*, 1934, **2**, 454; Clusius and Bartholomé, *Z. physikal. Chem.*, 1935, *B*, **30**, 237; Scott and Brickwedde, *Bull. Amer. Physical Soc.*, 1935, **10**, 9.
[14] Libby and Barter, *J. Chem. Physics*, 1942, **10**, 184.
[15] Bijl, *Physica*, 1937, **4**, 329; Hobbs, *J. Chem. Physics*, 1939, **7**, 318.
[16] See, for example, Mayer and Mayer, "Statistical Mechanics," John Wiley and Company, New York (1940), for a complete discussion of these functions and their derivation.
[17] Redlich, *Z. physikal. Chem.*, 1935, *B*, **28**, 371; see also W. R. Angus *et al.*, *J.*, 1936, 971. This theorem holds for each symmetry type as well as for all vibrations as stated here.
[18] Waldman (*Naturwiss.*, 1943, **31**, 205) has made a similar expansion of this function. Bigeleisen and Mayer (*J. Chem. Physics*, in the press) have expanded the function to secure

$$\ln \frac{Q_2}{Q_1} = \ln \frac{\sigma_1}{\sigma_2} + \Sigma_i \left(-\frac{1}{u_i} + \frac{1}{2} + \frac{1}{1 - e^{-u_i}} \right) \Delta u_i$$

and they have calculated tables giving values of the function in the parenthesis for values of u usually encountered. I am indebted to them for the use of these tables for many of these calculations.
[19] *Proc. Camb. Phil. Soc.*, 1928, **24**, 280.
[20] *Ibid.*, 1933, **29**, 142, 407.
[21] *J. Chem. Physics*, 1934, **2**, 65.
[22] *Chem. Reviews*, 1936, **18**, 277.
[23] Urey and Greiff, *loc. cit.*, ref. (12).
[24] *Loc. cit.*, ref. (10).
[25] Farkas and Farkas, *Trans. Faraday Soc.*, 1934, **30**, 1076; Bonhoeffer and Rummel, *Naturwiss.*, 1934, **22**, 45; Bonhoeffer, *Z. Elektrochem.*, 1934, **40**, 469.
[26] *J. Chem. Physics*, 1943, **11**, 101; Black and Taylor, *ibid.*, p. 395.
[27] See "Chemie der Deuteriumverbindungen," Tagungshefte der Deutschen Bunsen-Gesellschaft, p. 21 ff. (1938), for a review of these data.
[28] *Nature*, 1935, **135**, 229.
[29] Rosenthal, *Physical Rev.*, 1935, **47**, 236.
[30] I am indebted to Dr. Edward Teller and Dr. Maria G. Mayer for calling this method to my attention.
[31] The former authors report values of the C^{13}/C^{12} ratio from 1·013 to 1·022 above that for the carbon dioxide of the air for limestones, clam-shell, and sodium carbonate, while the latter authors report an average of 1·021 with no trend which they believe to be significant. The variation is probably not significant but, as we shall see, it is more difficult to account for the larger values. The variation is probably due to variations in the C^{13} content of air carbon dioxide, this variation being due to the low C^{13} content of coal and the presence of carbon dioxide from coal in the samples of air investigated.
[31a] In using equations (17) and (18) it is best to use average values for m and M, that is, 17 and 12·5 for oxygen and carbon respectively. It is possible to secure exact values for the frequencies of the isotopic oxygen molecule from assumed self-consistent values for the isotopic carbon molecule. Also, the frequencies of the $C^{12}O_2^{16}O^{18}$ molecule can be calculated in a similar way. Because of the errors due to unknown anharmonic terms, such calculations are hardly justified.
[32] This possibility was discussed by Professor Paul Niggli of Zürich when the author discussed this subject at the University of Zürich.
[33] *J. Amer. Chem. Soc.*, 1935, **57**, 2731; *J. Chem. Physics*, 1935, **4**, 268.
[34] Greene and Voskuyl, *J. Amer. Chem. Soc.*, 1936, **58**, 693; Hall and Johnson, *ibid.*, p. 1920; Jones and Hall, *ibid.*, 1937, **59**, 259; Smith and Matheson, *J. Res. Nat. Bur. Stand.*, 1936, **17**, 625.
[35] *Bull. Amer. Mus. Nat. Hist., New York*, 1946, **87**.
[36] See references given in the table. Also Smyth, "Atomic Energy for Military Purposes," Princeton University Press (1945).
[37] Pegram, Huffman, and Urey, *Ind. Eng. Chem.*, 1937, **29**, 531; Thode, Smith, and Walking, *Canadian J. Res.*, 1944, **22** *B*, 127. Also, Dr. Merle Randall has used this method for concentrating these isotopes.

PRESIDENTIAL ADDRESS.

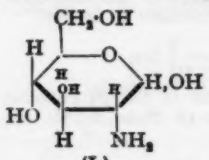
DELIVERED BEFORE THE CHEMICAL SOCIETY IN BIRMINGHAM ON APRIL 25TH, 1946.

Carbohydrate Components of Biologically Active Materials.

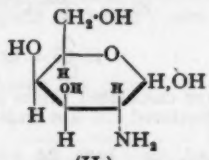
By W. N. HAWORTH, F.R.S.

THE inquiry into the structure and function of the carbohydrate components of biologically active products is being pursued by many workers. Some of the recent studies merit a more comprehensive review than I can give in the time at my disposal in this Presidential Address. In my present survey I propose to confine my attention to those carbohydrate components containing nitrogen as a substituent group. The number of sugar units which are attached to nitrogen in the complex molecule varies enormously in different cases, and other groups modifying the constituent sugar units are frequently present. Often these are high polymeric forms of carbohydrates occurring in combination with proteins or fats, and a classification of them includes mucopolysaccharides, mucoproteins, and mucolipoids originating in a wide variety of cells and especially in bacterial cells. A number of these products have been the subject of study here and elsewhere and a brief classification of many of them is given in the appendix to this Address.

In general these products are characterised by the presence of an amino-hexose unit, either chitosamine or chondrosamine; they have a low but significant protein content, and in aqueous solution the mucopolysaccharides show a high viscosity and tend to become insoluble in water after separation and dehydration. Our work here has revealed the identity of these amino-hexoses, and configurationally they are recognised respectively as 2-amino-glucose and 2-amino-galactose or as D-glucosamine (I) and D-galactosamine (II).



(I.)

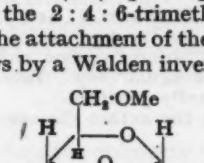


(II.)

These constitutional problems have long evaded solution because direct replacement of the amino-groups is accompanied by Walden inversion and treatment with nitrous acid leads to the anhydro-sugars such as chitose. It was suggested that chitosamine was 2-amino-mannose, whilst chondrosamine could be regarded either as 2-amino-talose or 2-amino-galactose.

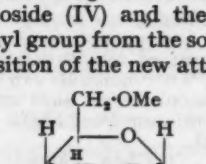
Biological activity is closely related to stereochemical arrangement, and it was important to refer these unique and characteristic units to the parent configurational sugar types. Experimentally this has been achieved in my laboratories by the synthesis of glucosamine and galactosamine derivatives through the anhydro-sugars which have been intensively studied over a number of years. A purely physical confirmation is provided by *X*-ray methods which Cox and Jeffrey applied in these laboratories. The isomorphism of the hydrochloride and hydrobromide of α-D-glucosamine enabled direct methods of calculation of electron densities to be employed and, independently of any previous stereochemical assumption, the atomic positions were determined with high precision (*Nature*, 1939, **143**, 984).

The chemical proof is founded on the initial observation that the derivative of 2 : 3-anhydro-mannoside (III) opens up its ethylene oxide ring in two ways with sodium methoxide to give both the 2 : 4 : 6-trimethyl methylglucoside (IV) and the 3 : 4 : 6-trimethyl methylaltroside (V), the attachment of the entering methyl group from the sodium methoxide being accompanied always by a Walden inversion at the position of the new attachment:



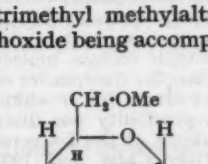
(III.)

NaOMe →



(IV.)

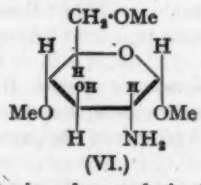
and



(V.)

By using ammonia in methyl alcohol instead of sodium methoxide for the ring fission it was found that the entering amino-group at position 2 in the formula corresponding to (IV) gave a crystalline derivative identical with a reference product of chitosamine, and therefore this product was

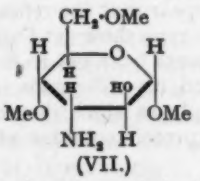
configurationally identified as a 2-amino-glucose (VI), and not 2-amino-mannose which would have the amino-group in the upper plane and not in the lower one. The two products (VI) and (VII) of the reaction with ammonia were therefore the following (Lake and Peat, and Peat and Wiggins, *J.*, 1938, 1417, 1810):



(VI.)

2-Amino-glucose derivative.

and

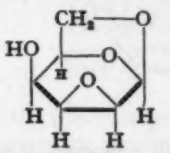


(VII.)

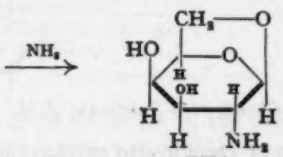
3-Amino-altrose derivative.

The entering anion attaches itself to the carbonium cation as the three-membered ring opens in either direction, and the Walden inversion occurs at the point of union of the anion.

During the current year a similar reaction has been successfully applied in the investigation of chondrosamine, a more recondite but equally important amino-hexose (James, F. Smith, Stacey, and Wiggins, *J.*, 1946, 625). Here the initial anhydro-sugar employed for the purpose was the dianhydride of talose (VIII) in which an anhydro-link was in positions 2 : 3, and another at 1 : 6, this latter not being concerned in the critical reaction:



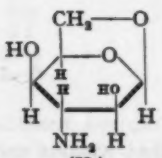
(VIII.)



(IX.)

2-Amino-galactose anhydride.

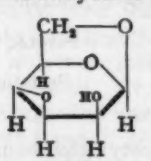
and



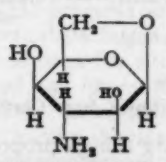
(X.)

3-Amino-idose anhydride.

In confirmation of the conclusion that (X) was 3-amino-idose, a similar experiment was conducted by using the 3 : 4-1 : 6-dianhydrotalose (XI) as the initial material. Here the entering amino-group at position 3 furnished 3-amino-idose anhydride identical with (X), and also 4-amino-mannose anhydride (XII) where the Walden inversion had occurred at position 4.

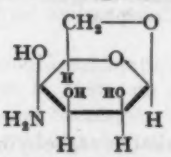


(XI.)



Identical with (X).

and



(XII.)

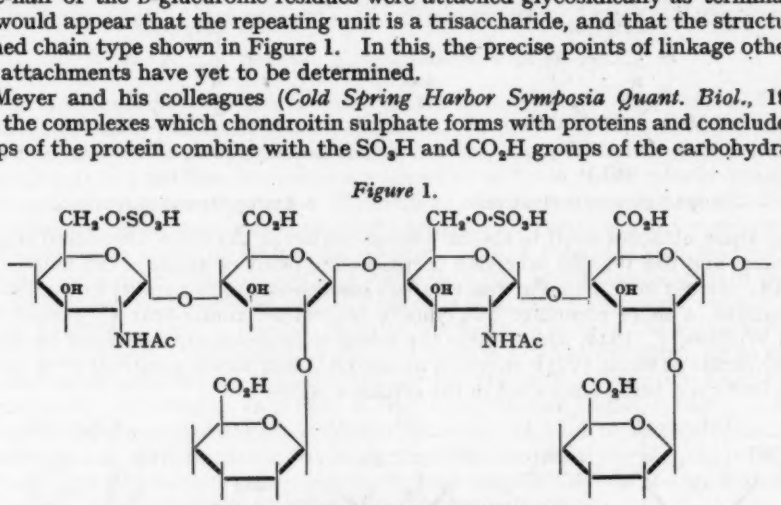
The 2-amino-galactose-1 : 6-anhydride (IX) was readily converted into 2-amino-galactose hydrochloride by using concentrated hydrochloric acid to open the 1 : 6-ring. Its identity with the naturally occurring chondrosamine hydrochloride was confirmed by an *X*-ray comparison of the two specimens. Inversion at the 1-position in this case would be immaterial in that mutarotation occurs in any event at this reducing position, and likewise it could not be apparent at the 6-position. The isolation of crystalline 2-amino-galactose hydrochloride from this sequence of changes is an achievement of the constitutional synthesis of chondrosamine, which is the analogue of glucosamine occurring in cartilaginous tissue and therefore a constituent unit in chondroitin sulphuric acid.

We have made some attempt to determine the molecular arrangement of this chondroitin sulphate. This is perhaps the most readily accessible sulphur-containing carbohydrate that occurs naturally, since it forms one of the major constituents of cartilaginous tissue from the trachea, nasal septa, aorta, etc. The first study on the nature of this complex acid carbohydrate was made by Schmiedeberg (*Arch. exp. Path. Pharm.*, 1889, **28**, 355) who gave a general idea of its type of structure. Levene, from his extensive investigations, considered that a derived sulphate-free substance "chondroitin" was a tetrasaccharide composed of two glucuronic acid residues conjugated with two units of chondrosamine, the whole then being esterified in the natural complex with sulphuric acid. The work of Bray, Gregory, and Stacey (*Biochem. J.*, 1944, **38**, 142) shows that this conception must now be modified. The Birmingham workers

prepared a methylated degraded chondroitin which was sulphate-free, and, from the hydrolysis of this, derivatives of *d*-glucuronic acid (including 2 : 3 : 4-trimethyl β-methyl-*d*-glucuronoside) and of chondrosamine (including *N*-acetyl 3 : 4 : 6-trimethyl methylchondrosaminide) were identified. About one-half of the D-glucuronic residues were attached glycosidically as terminal residues, so that it would appear that the repeating unit is a trisaccharide, and that the structure may be the branched chain type shown in Figure 1. In this, the precise points of linkage other than the glycosidic attachments have yet to be determined.

Karl Meyer and his colleagues (*Cold Spring Harbor Symposia Quant. Biol.*, 1938, 6, 99) examined the complexes which chondroitin sulphate forms with proteins and concluded that the NH_2 groups of the protein combine with the SO_3H and CO_2H groups of the carbohydrate. They

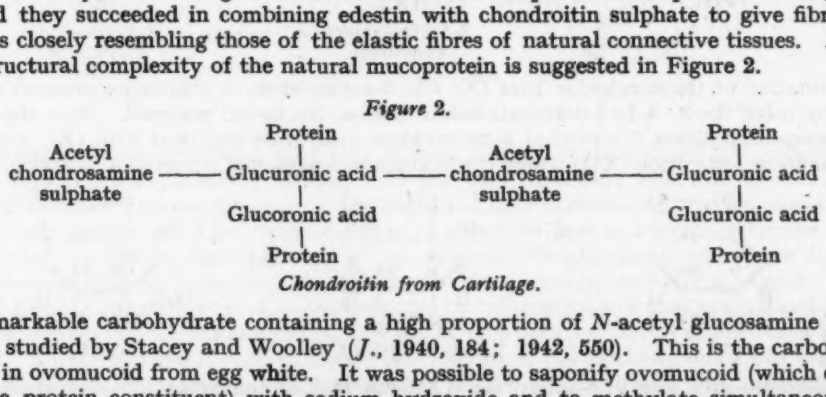
Figure 1.



Scheme for Chondroitin Sulphuric Acid.

suggested that hyaline cartilage is a salt of chondroitin sulphate with a protein of the gelatine type, and they succeeded in combining edestin with chondroitin sulphate to give fibres with properties closely resembling those of the elastic fibres of natural connective tissues. An idea of the structural complexity of the natural mucoprotein is suggested in Figure 2.

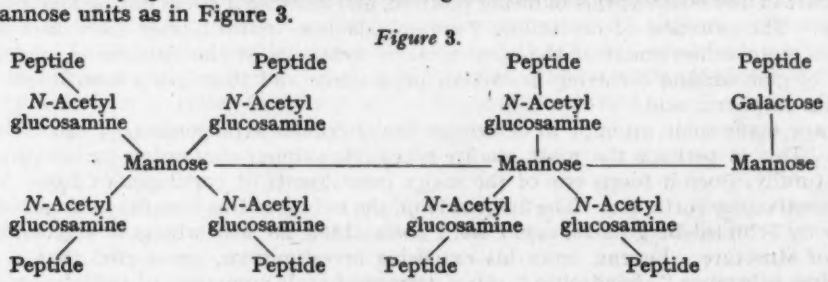
Figure 2.



Chondroitin from Cartilage.

A remarkable carbohydrate containing a high proportion of *N*-acetyl glucosamine residues has been studied by Stacey and Woolley (*J.*, 1940, 184; 1942, 550). This is the carbohydrate complex in ovomucoid from egg white. It was possible to saponify ovomucoid (which contains 80% of a protein constituent) with sodium hydroxide and to methylate simultaneously the carbohydrate residue with methyl sulphate to give an *N*-acetyl methyl derivative. Examination of the hydrolysis products of this revealed the remarkable result that by glycosidic attachment seven *N*-acetyl glucosamine units and one galactose unit radiate from a central core of three mannose units as in Figure 3.

Figure 3.



Ovomucoid.

In this representation the carbohydrate portion of the structure is shown not as a repeating unit but as the interior of one whole molecule and would thus be of relatively low molecular

weight. It would be equally possible to rearrange the peptide links to represent a much larger molecule of which the carbohydrate core is a repeating unit.

This work is of importance and may throw some light on problems connected with the occurrence of prosthetic carbohydrate groups in proteins, considered particularly from the immunological point of view.

One of the most fascinating and important fields of study of mucopolysaccharides containing amino-sugars and uronic acids is the group of bacterial polysaccharides, especially those which form the protective capsular material of the cell. The main reason for lack of rapid progress in this field is the expense and difficulty of obtaining sufficiently large amounts of authentic standardised material for chemical study. Some idea of the problems involved can be gathered from the recent enumeration by Boyd (" Fundamentals of Immunology ", 1943, Interscience Publishers) of more than 40 types of *Pneumococcus*, each possessing a different and well characterised capsular polysaccharide. Complex carbohydrates from these pneumococcus and other bacterial cells usually contain a certain proportion of nitrogen as shown in the table, which records some of our own findings.

Nitrogen Content of Polysaccharides of Bacterial Origin.

Polysaccharide from :	Nitrogen (%).
Type I *Pneumococcus*	5·5
Type IV *Pneumococcus*	6·0
Pneumococcus Somatic (Groups)	5·5
Bact. dysenteriæ (Shiga)	2—3
Bact. typhosum	2—3

Frequently this nitrogen owes its origin to the presence of constituent hexosamine units, although where the percentage is low, *e.g.*, 0·3%, there is usually found a small amount of a protein or a nucleic acid prosthetic group. The two nucleic acids, the ribo- and the deoxyribotypes account for the presence of pentoses and deoxypentoses in some bacterial polysaccharides, for very rarely are pentoses found to occur as monosaccharide units. A notable exception is in the case of two specific polysaccharides present in the tubercle bacillus which contains the rare pentose, D-arabinose. In addition, both of these polysaccharides contain hexosamine units, so that they present suitable types for study more especially since organisms causing tuberculosis can be grown on a standard and entirely synthetic medium in comparatively large quantities. We have recently been able to record some progress on the antigenic as well as on the haptenic polysaccharide constituents of this important pathogenic cell.

Probably no other single organism has been the subject of so much investigation as *Mycobacterium tuberculosis*. It was discovered and characterised by Koch in 1889 and the unique nature of the organism was soon recognised. In addition to the peculiar bacteriological properties of the four types of *M. tuberculosis* (human, bovine, avian, and cold-blooded) the chemical properties of their major constituents, polysaccharides, fats, and nucleoproteins have proved to be of unusual interest.

Although *M. tuberculosis* is readily killed by heat, it is relatively resistant to chemical attack, and this property has been ascribed in some measure to the presence of a waxy protective layer possessed by the organism. Recent American evidence (electron microscope) has confirmed an earlier opinion that the envelope is not uniform but has a granular texture, and although the question as to whether the tubercle organism possesses a true capsule is controversial (Dubos, " The Bacterial Cell ", Harvard University) we have shown that it does at least possess a surface layer. The waxy substances of which the layer is composed have been extensively investigated, more particularly by R. J. Anderson and his school (*Chem. Reviews*, 1941, **29**, 225). He has found that the lipoids occurring in these acid-fast bacteria are built on quite a different plan from those found in plants and animals and that their composition is more complex. Lipoids contained in five different strains of the human tubercle bacillus have been examined, together with those from the bovine and avian types, the so-called leprosy bacillus, and the non-pathogenic timothy glass bacillus, all grown on the Long synthetic medium. The interesting discovery was made that the fat of the human strain is not a glyceride, and the ordinary definition of a fat will need extension to include these new observations. The disaccharide trehalose takes the place of glycerol as the water-soluble component of the fat, whilst the fatty acids include new and hitherto unknown members such as tuberculostearic (10-methylstearic) and phthioic acids (see below).

Similarly, the phosphatides reveal new combinations in which the glycerophosphoric acid

occurring in plants and animals is partly replaced by a phosphorylated polysaccharide or glycoside; choline and aminoethyl alcohol appear to be absent.

Again, the waxes of these acid-fast bacteria are quantitatively important and are novel in composition since they are mainly esters in which optically active hydroxy-acids are combined with carbohydrates instead of with the usual alcohols. The wax from the human strain contains a specific polysaccharide, not found in waxes from other strains which often contain trehalose, and in the leprosy bacillus wax the alcohol is glycerol. Noteworthy among the optically active hydroxy-acids concerned in this combination in the human strain is mycolic acid $C_{88}H_{176}O_4$—a remarkably high molecular weight—and probably the property of acid-fastness in the bacilli is attributable to this component. For these and other outstanding researches we are indebted to R. J. Anderson and his co-workers.

As indicated below we have elucidated part of the structure of a polysaccharide obtained from the somatic portion of the cell after removal of the waxy layer. The polysaccharide behaved as a haptene and reacted with immune serum from tuberculous patients in high dilution (1 : 2,000,000). Some of the fatty acids are of profound interest since on injection into animals they are able to stimulate giant-cell and tubercle formation.

Recently a structural investigation of the complex mixture of fatty acids was undertaken by Sir Robert Robinson and N. Polgar (*J.*, 1945, 389). Phthioic acid, one of the specific cellular stimulants responsible for tubercle formation, has been shown to have the following structure :

$$CH_3\cdot[CH_2]_3\cdot CHMe\cdot[CH_2]_3\cdot CHMe\cdot[CH_2]_9\cdot CHMe\cdot CH_2\cdot CO_2H$$

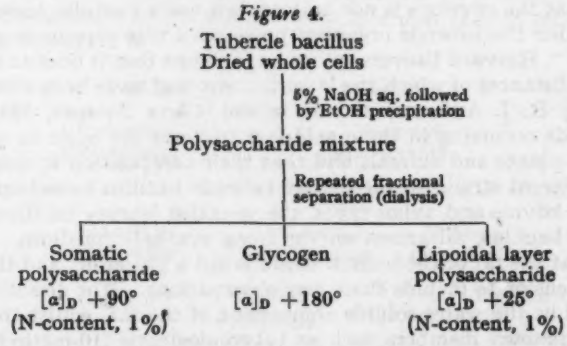
Phthioic (3 : 13 : 19-*Trimethyltricosanoic*) *Acid.*

The literature contains many references to polysaccharides which have been isolated from the cells and also from the culture medium remaining after the organisms have been grown. From the latter source, polysaccharides were found in close association with deoxyribonucleic acid and " tuberculin " protein, the latter being the active agent in the well-known specific skin test. The problem of separation of the major components of tuberculin, using the Tiselius apparatus, was investigated in great detail by Seibert and her co-workers (*Chem. Reviews*, 1944, **34**, 107).

A variety of specific polysaccharide fractions has been isolated from the whole bacterial cell by various workers; the fractions have widely different properties and serological activities, though in many cases there is reason to doubt the homogeneity of certain fractions. Tuberculosis glycogen has been separated from the polysaccharides of the cell, and measurements of its molecular size were made in the ultra-centrifuge (Chargaff and Moore, *J. Biol. Chem.*, 1944, **155**, 493) although the quantity available was insufficient to permit of an end-group assay. The glycogen assumed a characteristic red colouration with iodine, but it was noted that enzymic degradation with amylase proceeded more slowly than in the case of liver glycogen.

Here with my colleagues Stacey and Kent we have investigated the carbohydrate content of the outer lipoidal layer of the bacillus as well as that of the inner or somatic region. Two distinctive polysaccharides of different rotatory power are recognisable as well as the more common polysaccharide, glycogen. The two former are haptens which react in a dilution of well over one in a million with serum from tuberculous patients. They appear similar to those isolated by Heidelberger and his colleagues by other methods (*J. Biol. Chem.*, 1937, **118**, 79). The scheme of isolation, shorn of all but essential details, is outlined in Figure 4.

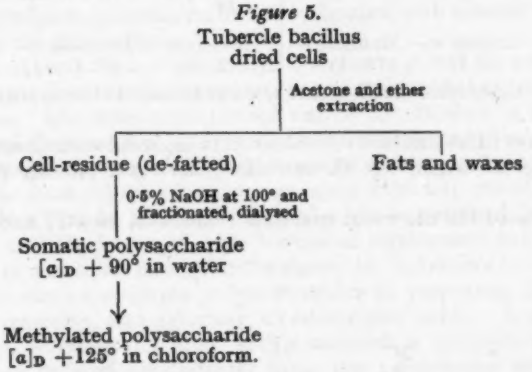
Figure 4.



It was apparent that an alternative route to the isolation of the somatic polysaccharide lay through the extraction by ether and acetone of all materials of the lipoidal or waxy layer. The

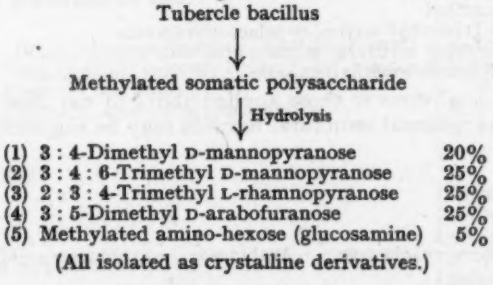
de-fatted cell-residue was then passed through the same procedure as that outlined in the above scheme. There was then isolated what appeared to be only the somatic polysaccharide ($[\alpha]_D$ + 90° in water); the methyl ether derivative, having $[\alpha]_D$ + 125° in chloroform, gave a quantitative separation of hydrolysis products, all of them in the form of crystalline compounds.

Figure 5.



The haptenic polysaccharide obtained by vigorous saponification methods from the somatic part of the cell after removal of the waxy layer (Figure 5) also contains an amino-sugar, mannose, L-rhamnose, and a D-arabinose constituent, and this structure of the polysaccharide has been investigated in some detail. The methyl ether, $[\alpha]_D$ + 125°, obtained in good yield, is readily hydrolysed with methanolic hydrogen chloride. From the hydrolysis mixture the constituents as shown in Figure 6 were characterised and identified.

Figure 6.


Tubercle bacillus
Methylated somatic polysaccharide
Hydrolysis
(1) 3 : 4-Dimethyl D-mannopyranose 20%
(2) 3 : 4 : 6-Trimethyl D-mannopyranose 25%
(3) 2 : 3 : 4-Trimethyl L-rhamnopyranose 25%
(4) 3 : 5-Dimethyl D-arabofuranose 25%
(5) Methylated amino-hexose (glucosamine) 5%
(All isolated as crystalline derivatives.)

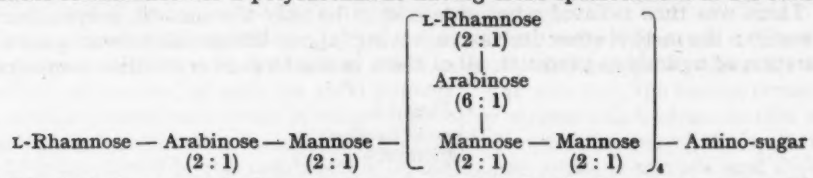
It is possible to speculate on the complete formulation of this polysaccharide; some interesting points are clear and the possible structural types can be suggested. The molecule is evidently highly branched since some of the mannopyranose units are linked through the 1 and 2 positions, while others are linked through the 1, 2, and 6 positions.

The whole of the L-rhamnose residues are in the pyranose form and constitute terminal units linked glycosidically to the rest of the molecule. The existence of L-rhamnose in this complex has not previously been recognised, and the points of union of each of the sugar units are given for the first time. The arabinose units are of great interest. Other workers (Heidelberger and Anderson) have shown that tuberculosis polysaccharides contain D-arabinose units, but I am able to announce the first recorded isolation of D-arabofuranose from this or indeed any other natural source. The arabofuranose units are all linked through the 1 and 2 positions. Preliminary results seem to indicate that the amino-sugar closely resembles D-glucosamine, so that this important amino-hexose plays a ubiquitous role in the composition of many carbohydrates of biologically active materials.

The proportions of the constituents actually isolated are as follows:

D-Mannopyranose	linked	through	the 1, 2, and 6	positions	: 4-parts.
,,	,,	,,	1 and 2	,,	: 5 ,,
D-Arabofuranose	,,	,,	1 and 2	,,	: 5 ,,
D-Rhamnopyranose	,,	,,	1 position	,,	: 1 ,,
Partly methylated 2-amino-sugar, linkage unknown					: 1 ,,

A possible formulation for a polysaccharide having these specifications is the following :

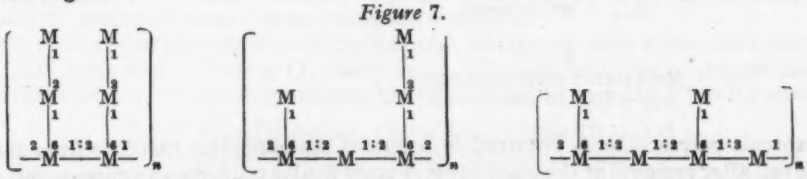


Graded hydrolysis or acetolysis methods are needed to decide the more exact positions of the constituent units.

There is a general structural similarity between this mannose-containing polysaccharide and mannans of microbiological origin, *e.g.* those from yeasts and moulds though these are less complex.

Some possible structures for the yeast mannan (Haworth, Heath, and Peat, *J.*, 1941, 833) are shown in Figure 7.

Figure 7.



The polysaccharide from the lipoidal layer (see Figure 4) was also submitted to constitutional study through its methyl ether. Hydrolysis led to the isolation and quantitative estimation of crystalline derivatives of the following components in their glycosidic forms :

	Molecular ratio.
2 : 3 : 5-Trimethyl methyl-D-arabofuranoside	2·05
3 : 5-Dimethyl ,, ,, ...	5·3
2 : 3 : 6-Trimethyl methyl-D-galactopyranoside	4·7
3 : 4-Dimethyl methyl-D-mannopyranoside	2·1
Dimethyl amino-methylhexoside	1·0

From considerations analogous to those applied above in the case of the somatic polysaccharide a possible and provisional structural formula may be suggested for this carbohydrate.

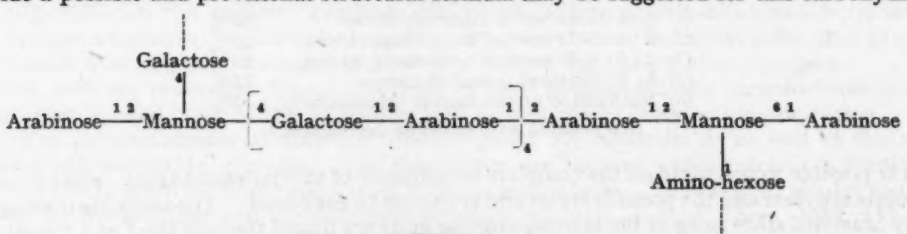
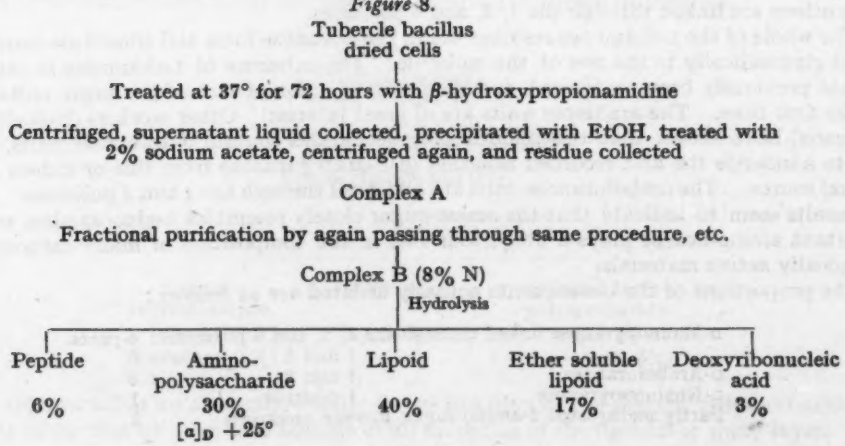


Figure 8.


Tubercle bacillus dried cells
Treated at 37° for 72 hours with β-hydroxypropionamidine
Centrifuged, supernatant liquid collected, precipitated with EtOH, treated with 2% sodium acetate, centrifuged again, and residue collected
Complex A
Fractional purification by again passing through same procedure, etc.
Complex B (8% N)
Hydrolysis
Peptide 6%
Amino-polysaccharide 30% [α]D +25°
Lipoid 40%
Ether soluble lipoid 17%
Deoxyribonucleic acid 3%

The polysaccharide from the waxy layer was bound in a novel complex which had some interesting serological properties. This complex was possibly an antigen which, in addition to the polysaccharide (*a*), contained (*b*) an acid-fast lipoid material, (*c*) deoxyribonucleic acid, and (*d*) a small amount of a peptide constituent, and it could be obtained only from the intact cells. The complex was extracted at 37° as shown in Figure 8 by organic lipophilic bases (including urea and β-hydroxypropionamidine), further fractionated with organic bases, and finally isolated by being dried from the frozen state.

For the serological tests the materials, *e.g.*, Complexes A and B, were both separately coated on to a colloidal suspension of collodion particles and then tested against the sera of tuberculous and normal humans. The tests were carried out by Dr. Nassau of the Harefield Sanatorium and are being extended elsewhere. The collodion particles coated with Complex A and B give a good agglutination under appropriate conditions with sera from tuberculous patients, and already the results appear to show promise in diagnosis apart from any possible value in immunisation. It is of interest to note that no antigenic material could be obtained from defatted cells.

Other complex carbohydrates of high biological significance are the specific blood group factors, an account of which has been given by Stacey in "Advances in Carbohydrate Chemistry". Group A resembles the tuberculosis polysaccharides in possessing branched chain structures with glucosamine, mannose, and galactose, as constituent units. A specimen examined (Bray, Henry, and Stacey, *Biochem. J.*, 1946, 124) contained a methylpentose end-group, namely L-fucose, which thus differed significantly from the L-rhamnose end group in the tubercle polysaccharide described above.

It will be seen that many projects in the carbohydrate field still await the attention of workers interested in the problems of infectious disease processes, and it is worthy of mention that American investigators have isolated from the important antibiotic, streptomycin, the optical enantiomorph of glucosamine, namely the L-isomer.

Appendix.

	Identified products of acid hydrolysis of carbohydrate portion.
1. *Containing hexosamine and hexuronic acid.*	
(a) Sulphate-free.	
(i) Hyaluronic (from vitreous humour, umbilical cord, synovial fluid, ovarian tumour, Group "A" hæmolytic *Streptococcus* and skin).	*N*-Acetyl D-glucosamine Hexuronic acid (probably D-glucuronic acid)
(ii) Type I *Pneumococcus* specific polysaccharide.	Acetic acid Hexosamine D-Galacturonic acid
(b) Sulphate-containing.	
(i) Heparin.	Sulphuric acid D-Glucuronic acid D-Glucosamine (unacetylated)
(ii) Chondroitin sulphate.	*N*-Acetyl chondrosamine Sulphuric acid D-Glucuronic acid
(iii) Mucoitin sulphate (from gastric mucin).	*N*-Acetyl D-glucosamine Hexuronic acid Sulphuric acid
(iv) Hyaluronic acid sulphate (from the cornea).	Sulphuric acid *N*-Acetyl hexosamine Hexuronic acid
2. *Containing hexosamine but no hexuronic acid.*	
(a) Chitin.	*N*-Acetyl D-glucosamine
(b) Bacterial.	
(i) *Pneumococcus* "C" (or Group) polysaccharide.	*N*-Acetyl amino-sugar D-Glucose
(ii) Type IV *Pneumococcus* specific polysaccharide.	*N*-Acetyl amino-sugar D-Glucose
(iii) Type XIV specific polysaccharide.	*N*-Acetyl D-glucosamine D-Galactose
(c) Blood Group.	
(i) Blood Group A carbohydrate (from saliva, pepsin, urine, gastric mucin, pancreas, etc.).	*N*-Acetyl D-glucosamine D-Mannose D-Galactose L-Fucose
(ii) Blood Group B and O carbohydrates from human saliva and gastric mucin.	Hexosamine

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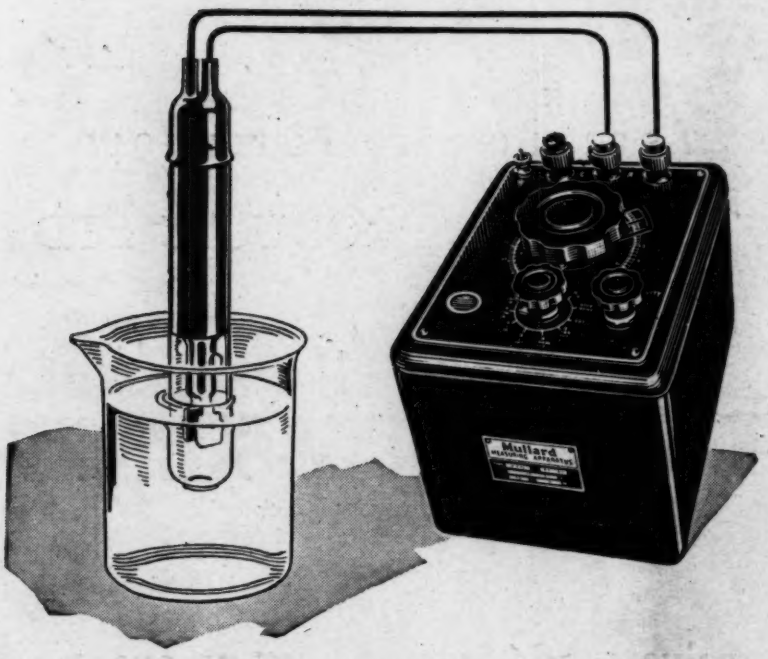

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